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PRINCIPAL INVESTIGATOR:
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CONTRACTING ORGANIZATION:
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14. ABSTRACT
The Behavioral Center had three primary Objectives all of which were achieved: 1) To support an integrated, interdisciplinary Program of Research consisting of three synergistic Research Projects each of which addresses an important issue in breast cancer genetic research with African-American women that entails critical psychological or behavioral issues. Thus, our first purpose was to do outstanding research, with implications for our understanding of the etiology of breast cancer, as well as for our understanding of behavior per se. 2) To encourage the development of truly interdisciplinary thinking among the faculty involved in the Program of Research that can serve as a model for other institutions. Thus, our second purpose was to show by example, not only the utility of an interdisciplinary approach (synergy with Objective 1), but one approach that may facilitate its achievement - working together on an integrated project that addresses important issues of interest to all members of the research team. We proposed to bridge the gap between biobehavioral research and epidemiologic approaches. 3) To facilitate the development of interdisciplinary perspectives among new investigators in breast cancer research. Thus, our third purpose was to provide interdisciplinary training through both didactic and hands-on research, as well as informal seminars to outstanding young investigators likely to represent the future of the field.

15. SUBJECT TERMS
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Table of Contents

Genetic Factors in Breast Cancer: Center for Interdisciplinary Behavioral Research

Principal Investigator: Dr. Dana H. Bovbjerg

Introduction

The overarching goal of the Breast Cancer Behavioral Center of Excellence in the Department of Oncological Sciences of the Mount Sinai School of Medicine was an exploration of the reciprocal interactions between genetic aspects of breast cancer and biopsychosocial factors, with a particular emphasis on African-American women. While African-American women are overall less likely to develop breast cancer than White women, they are significantly more likely to develop aggressive early-onset breast cancer (1-4). African-American women are also more likely to die of breast cancer (1, 2, 5, 6). The causes of these health disparities with regard to breast cancer have yet to be well elucidated, but are likely to involve a complex interplay between genetic factors and biopsychosocial factors at molecular, cellular, personal and societal levels (2, 5, 7, 8).

The Breast Cancer Behavioral Center of Excellence supported an integrated, interdisciplinary Program of Research including three synergistic Research Projects each of which addresses an important issue in breast cancer genetic research that entailed critical psychological or behavioral issues that may be particularly relevant for African-American women. The Center had three primary objectives: Objective 1: To do outstanding research, with implications for our understanding of the etiology of breast cancer, as well as for our understanding of behavior per se. Objective 2: To encourage the development of productive interdisciplinary thinking among the faculty involved in the Program of Research that can serve as a model for other institutions. We proposed to show by example, not only the utility of an interdisciplinary approach (synergy with Objective 1), but one approach that may facilitate its achievement - working together on an integrated project that addresses important issues of interest to all members of the research team. As part of that effort, we proposed to bridge the gap between biobehavioral research and epidemiologic approaches. Objective 3: To facilitate the development of truly interdisciplinary perspectives among new investigators in breast cancer research. As part of that effort, we proposed to provide interdisciplinary training through both didactic and hands-on (synergy with Objective 1) research, as well as informal seminars (synergy with Objective 2) to outstanding young investigators likely to advance the field in the future. All of these objectives were achieved as is documented below.

The Behavioral Center's interdisciplinary research efforts to explore this complex topic were grounded in the biobehavioral model of health and disease. According to this theoretical perspective, what people think and feel affects the state of their health in at least two basic ways: 1) by affecting their behavioral choices (e.g., including those for primary prevention (e.g., alcohol consumption), secondary prevention (e.g., following cancer screening guidelines) and tertiary prevention (e.g., following treatment schedules)), and 2) by affecting their biological processes (e.g., increased cortisol levels with stress), each of which is controlled by the central nervous system (7, 9-13) A better understanding of the interactions between biobehavioral factors and the genetic aspects of breast cancer may thus have profound implications for cancer prevention and control, as it may suggest novel strategies to reduce the threat posed by this disease to African-American women and other underserved populations (14-19).

The three synergistic Projects in the MSSM Behavioral Center of Excellence (and four supporting Cores) applied a biobehavioral perspective to three distinct loci where such factors are likely to impact genetic issues in breast cancer:

Project 1, "Behavior, estrogen metabolism, and breast cancer risk: A molecular epidemiologic study" (Ambrosone, PI)—Psychological, behavioral, and endocrine factors were investigated as potential etiological agents in the development of breast cancer, operating through interactions with underlying genetic factors.

Project 2, "Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA decision making among women with breast cancer" (Valdimarsdottir, PI)--Cultural, psychological and behavioral factors were investigated for their potential impact on patients decisions regarding genetic testing for breast cancer susceptibility.

Project 3, "Immune surveillance, stress, and inherited susceptibility to breast cancer: A psychobiological analysis of the healthy daughters of breast cancer patients" (Bovbjerg, PI)--Psychological and behavioral factors were investigated as sources of variability in phenotypic expression of possible biological pathways involved in familial risk of breast cancer, such as immune surveillance mechanisms.

All three Projects were synergistic with one another both theoretically and practically (e.g., Project 1 served as entry point for participants for Projects 2 & 3) and each Project used all of the Cores, which were dedicated to:

Core A: Recruitment, Tracking, and Interviewing;
Core B: Molecular Diagnostic and Research;
Core C: Biostatistics and Data Management;
Core D: Training.

In addition to supporting the three original projects, the Center also served as a catalyst for the development of several related research studies, which were funded by independent NCI and DOD awards that interacted both intellectually (related goals, shared investigators, shared measures) and in some cases, practically (shared participants), with the three projects in the Center. Perhaps most notably, the Center also played an instrumental role in the development of another DOD funded Center at Columbia University Medical College (Neugut, PI) by providing intellectual input (Bovbjerg and Ambrosone are co-investigators) and critical practical support, as well as serving as a referral source for recently diagnosed African-American breast cancer patients that are the focus of that Center's research efforts.

Body

In April 2004, we received official notification of approval of the HSRRB of the USAMRAA for all of the proposed three Projects. Thus we were able to begin recruiting to each of the three projects. However, because the recruitment of participants to Project 2 and Project 3 were entirely dependent on Project 1 for initial identification, recruitment, and assessment of participants the latter two projects were further delayed. In addition, because of the delay in receiving the initial approval, as well as subsequent delays in receiving approvals for modifications to the protocol to improve the science, as well as to reduce burden and enhance recruitment efforts, we remained substantially behind our anticipated timeline for completion of the tasks listed in the Statements of Work (SOW) for each of the Projects and Cores (as detailed for each Project and Core in separate sections below). In June 2005, we submitted a Request for Supplemental Funding in order to: 1) bring to fruition the three integrated projects originally supported by the Center; 2) enable the full multiplier effect of the Center on three related, independently funded DOD studies (Idea Awards); and 3) ensure the success of a newly funded

DOD Center of Excellence at Columbia University Medical Center examining racial disparities in the initiation and intensity of adjuvant therapy for breast cancer. We were granted a two-year extension (Amendment # P00004). In November 2007, we had a teleconference with DOD representatives to discuss the status of the work and made consensual modifications to the Statements of Work based on review of the recent research literature, initial data, and changing exigencies of the front line research effort, particularly the impact of related funded projects that built upon the base established by the Center. This report therefore focuses on the revised SOW.

Key Research Accomplishments

The three Primary Objectives of the Center for Interdisciplinary Biobehavioral Research on Genetic factors in Breast Cancer were met. With Center support: 1) interdisciplinary biobehavioral research regarding genetic factors in breast cancer, with important implications for our understanding of the etiology of breast cancer was conducted; 2) interdisciplinary thinking among the faculty involved in the Program of Research was productively developed and served as a model for other institutions; 3) interdisciplinary perspectives were fostered among promising new investigators in breast cancer research. Specific accomplishments for each Project are detailed below. The strongest evidence that these three objectives were met is provided by the track record of funded peer-reviewed funded research projects that were developed as a result of Center activities (see below).

Reportable Outcomes

Grants: The Center has provided the interdisciplinary intellectual environment, background and data for the development for a number of peer-reviewed grants that have been funded to address additional scientific questions related to breast cancer. These grants include:

- DAMD17-02-1-0501 (Bovbjerg, PI) 7/22/02-7/21/08
  Project Title: **"**Immune Surveillance, Cytokines, and Breast Cancer Risk: Genetic and Psychological Influences in African American Women"
- R01 CA10059 (Ambrosone, PI; Bovbjerg Co-I) 7/1/04 – 6/30/10
  Project Title: "Race & Risk Factors for Early Aggressive Breast Cancer"
- BC031275 (Valdimarsdottir, PI; Bovbjerg, Co-PI) 7/01/04-6/30/08
  Project Title: "Emotional, Biological and Cognitive Impact of a Brief Expressive Writing Intervention for African American Women at Familial Breast Cancer Risk"
- BC009027 (Neugut, PI; Bovbjerg, Site-PI) 03/1/05-02/28/10
  Project Title: "Causes of Racial Disparities in the Optimal Receipt and Compliance with Adjuvant Systemic Therapy for Breast Cancer"
- DAMD 17-03-1-0454 (Thompson, PI) 6/9/05-6/8/08
  Project Title: "Increasing Breast Cancer Surveillance Among African American Breast Cancer Survivors"
- BC074340/W81XWH-08-1-0379 (Zhao, PI; Ambrosone,Co-I) 6/01/08-5/31/11
  Project Title: "microRNAs: Novel Breast Cancer Susceptibility Factors in Caucasian and African American Women"
- BC075007/ W81XWH-08-1-0383 (Haiman, PI; Ambrosone, Site PI) 7/01/08-6/30/12
  Project Title: "A genome-wide breast cancer scan of African-American women"
- R01 CA128557 (Bovbjerg, PI) 9/1/08-7/31/13
  Project Title: "Breast Cancer Risk: Analysis of Heightened HPA Axis Stress Responsivity"

- Breast Cancer Research Foundation (Ambrosone, PI) 10/1/08 – 09/30/10
  Project Title: "Basal-Like Breast Cancers in Black and White Women: An 'Out of Africa' Hypothesis"
- KG080165 (Ziv, PI; Ambrosone, Site PI) 12/8/08 – 12/7/11
  Project Title: "Admixture Mapping for Breast Cancer Susceptibility Genes Among African American Women"
- R01 CA1332641 (Ambrosone, PI) 04/1/10 – 03/31/14
  Project Title: "DNA Methylation: a Mechanism for Aggressive Breast Cancer in African-American Women?"
- P01 CA151135-01* *submitted* (Ambrosone, PI) 7/1/10 – 6/30/15
  Project Title: "Epidemiology of Breast Cancer subtypes in African American Women: a Consortium"

Manuscripts: The Center has also provided the background, resources and data for a number of manuscripts, some of which are now published peer-reviewed papers in the literature. These manuscripts include:

- Dettenborn L, James GD, van Berge-Landry H, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH: Heightened cortisol responses to daily stress in working women at familial risk for breast cancer, Biol Psychol 2005; 69(2):167-79. PMID: 15804544.
- Erblich J, Brown K, Kim Y, Valdimarsdottir HB, Livingston BE, Bovbjerg DH: Development and validation of a Breast Cancer Genetic Counseling Knowledge Questionnaire, Patient Educ Couns 2005; 56(2):182-91. PMID: 15653247.
- Kim Y, Duhamel KN, Valdimarsdottir HB, Bovbjerg DH: Psychological distress among healthy women with family histories of breast cancer: effects of recent life events, Psychooncology 2005; 14(7):555-63. PMID: 15543540.
- Amend K, Hicks D, Ambrosone CB: Breast cancer in African-American women: Differences in tumor biology from European-American women, Cancer Res 2006; 66:8327-30.
- Dettenborn L, James GD, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH: Breast cancer-specific intrusions are associated with increased cortisol responses to daily life stressors in healthy women without personal or family histories of breast cancer, J Behav Med 2006; 29(5):477-85. PMID: 16944305.
- DiLorenzo TA, Schnur J, Montgomery GH, Erblich J, Winkel G, Bovbjerg DH: A model of disease-specific worry in heritable disease: the influence of family history, perceived risk and worry about other illnesses, J Behav Med 2006; 29(1):37-49. PMID: 16470344.
- Jandorf L, Fatone A, Borker PV, Levin M, Esmond WA, Brenner B, Butts G, Redd WH: Creating alliances to improve cancer prevention and detection among urban medically underserved minority groups - The East Harlem Partnership for Cancer Awareness, Cancer 2006; 107(8):2043-51.
- Thompson HS, Littles M, Jacob S, Coker C: Cancer survivors of African descent posttreatment breast cancer surveillance and follow-up care experiences of breast - An exploratory qualitative study, Cancer Nurs 2006; 29(6):478-87.
- Choi JY, Nowell SA, Blanco JG, Ambrosone CB: The role of genetic variability in drug metabolism pathways in breast cancer prognosis, Pharmacogenomics 2006; 7(4):613-24.

- Ambrosone, CB: The promise and limitations of genome-wide association studies to elucidate the causes of breast cancer, Breast Cancer Res 2007; 9(6):114.
- Chanda P, Sucheston L, Zhang A, Brazeau D, Freudenheim JL, Ambrosone C, Ramanathan M: AMBIENCE: A Novel Approach and Efficient Algorithm for Identifying Informative Genetic and Environmental Associations With Complex Phenotypes, Genetics 2008; 180 (2):1191-1210.
- Ambrosone CB, Kropp S, Yang J, Yao S, Shields PG, Chang-Claude J: Cigarette smoking, N-acetyltransferase 2 genotypes, and breast cancer risk: Pooled analysis and meta-analysis, Cancer Epidemiol Biomarkers Prev 2008; 17(1):15-26.
- Dettenborn L, James GD, Britton JA, Bovbjerg DH: Higher levels of central adiposity in healthy premenopausal women with family histories of premenopausal breast cancer, Am J Hum Biol 2008; 20(3):355-8. PMID: 18161037.
- James GD, Gastrich HJ, Valdimarsdottir HB, Bovbjerg DH: The rate of urinary cortisol excretion at work is persistently elevated in women at familial risk for breast cancer, Am J Hum Biol 2008; 20(4):478-80. PMID: 18257060.
- Edwards TA, Thompson HS, Kwate NO, Brown K, McGovern MM, Forman A, Kapil-Pair N, Jandorf L, Bovbjerg DH, Valdimarsdottir HB: Association between temporal orientation and attitudes about BRCA1/2 testing among women of African descent with family histories of breast cancer, Patient Educ Couns 2008; 72(2):276-82.
- Cheng C-Y, Kao WHL, Patterson N, Tandon A, Haiman CA, Ziv E, Harris TB, Xing C, Ambrosone CB, John EM, Brancati FL, Coresh J, Bandera E, Jandorf L, Ciupak G, Parekh RS, Klag MJ, Meoni LA, Hsueh W-C, Fejerman L, Pawlikowska L, Freedman ML, Nalls MA, Akylbekova EL, Orwoll ES, Tennille S. Leak TS, Li R, Miljkovic-Gacic I, Ursin G, Bernstein L, Ardlie K, Cummings SR, Taylor SA, Boerwinckle E, Zmuda JM, Henderson BE, Wilson JG, Reich D: Admixture mapping of 15,280 African Americans finds obesity loci on chromosome 5 and X, PLoS Genetics 2009; 5(5):e1000490. PMCID: PMC2679192
- Sussner KM, Thompson HS, Jandorf L, Edwards TA, Forman A, Brown K, Kapil-Pair N, Bovbjerg DH, Schwartz MD, Valdimarsdottir HB: The influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing for breast cancer among women of African descent, Psychooncology 2009; 18(9):945-55.
- Thompson HS, Edwards T, Erwin DO, Lee SH, Bovbjerg D, Jandorf L, Littles M, Valdimarsdottir HB, Lewis T, Karsif K, Petersen B, Romero J: Training lay health workers to promote post-treatment breast cancer surveillance in African American breast cancer survivors: development and implementation of a curriculum, J Cancer Educ 2009; 24(4):267-74.
- Rini C, O'Neill SC, Valdimarsdottir H, Goldsmith RE, Jandorf L, Brown K, DeMarco TA, Peshkin BN, Schwartz MD: Cognitive and emotional factors predicting decisional conflict among high-risk breast cancer survivors who receive uninformative BRCA1/2 results, Health Psychol 2009; 28(5):569-78.
- Choi JY, James SR, Link PA, McCann SE, Hong CC, Davis W, Nesline MK, Ambrosone CB, Karpf AR: Association between global DNA hypomethylation in leukocytes and risk of breast cancer, Carcinogenesis 2009; 30(11):1889-97.
- McCarty KM, Santella RM, Steck SE, Cleveland RJ, Ahn J, Ambrosone CB, North K, Sagiv SK, Eng SM, Teitelbaum SL, Neugut AI, Gammon MD: PAH-DNA Adducts,

Cigarette Smoking, GST Polymorphisms, and Breast Cancer Risk, Environ Health Perspect 2009; 117(4):552-8.

- Shen J, Ambrosone CB, Zhao H: Novel genetic variants in microRNA genes and familial breast cancer, Int J Cancer 2009; 124(5):1178-82.
- Fejerman L, Haiman CA, Reich D, Tandon A, Deo RC, John EM, Ingles SA, Ambrosone CB, Bovbjerg DH, Jandorf LH, Davis W, Ciupak G, Whittemore AS, Press MF, Ursin G, Bernstein L, Huntsman S, Henderson BE, Ziv E, Freedman ML: An admixture scan in 1,484 African-American women with breast cancer, Cancer Epidemiol Biomarkers Prev 2009; 18:3110-7. PMCID: PMC2783219
- Goldsmith RE, Jandorf L, Valdimarsdottir H, Amend KL, Stoudt BG, Rini C, Hershman D, Neugut A, Reilly JJ, Tartter PI, Feldman SM, Ambrosone CB, Bovbjerg DH: Traumatic stress symptoms and breast cancer: the role of childhood abuse, Child Abuse and Neglect 2010; 34:465-70.
- Ambrosone CB, Ciupak GL, Bandera EV, Jandorf L, Bovbjerg DH, Zirpoli G, Pawlish K, Godbold J, Furberg H, Fatone A, Valdimarsdottir H, Yao S, Li Yulin, Hwang H, Davis W, Roberts M, Sucheston L, Demissie K, Amend KL, Tartter P, Reilly J, Pace BW, Rohan T, Sparano J, Raptis G, Castaldi M, Estabrook A, Feldman S, Weltz C, Kemeney M: Conducting molecular epidemiological research in the age of HIPAA: A multi-institutional case-control study of breast cancer in African-American and European-American women, J Oncology; EPub 2009 Oct 25. *In press*
- Chen GK, Stram DO, Millikan RC, Ambrosone CB, John EM, Bernstein L, Palmer JR, Zheng W, Hu JJ, Rebbeck TR, Ziegler RG, Chen F, Nyante S, Bandera EV, Ingles SA, Press MF, Rosenberg L, Deming SL, Rodriguez-Gil JL, DeMichele A, Chanock SJ, Olopade OI, Hua D, Edlund CK, Wan P, Sheng X, Pooler LC, Van Den Berg DJ, Le Marchand L, Kolonel LN, Henderson BE, Haiman CA: Towards understanding genetic susceptibility for breast cancer in African-American women: a novel locus at 5q31. *Submitted*
- Chen GK, Millikan RC, John EM, Ambrosone CB, Bernstein L, Zheng W, Hu JJ, Ziegler RG, Henderson BE, Haiman CA, Stram DO: Enhancing the power of genetic association studies through the use of publicly available genotype data. *Submitted*

Contribution to scientific conferences: The Center has also provided the background, resources and data for a number of abstracts, posters, and papers included in scientific conferences. These include:

- Forman A, Kapil-Pair N, Rowse J, Farrell E, Brown K, Jandorf L, Thompson H, Valdimarsdottir, H: Development of a culturally tailored interactive decision aid for BRCA1/2 testing for African American women. National Society of Genetic Counselors 24th Annual Education Conference. (2005)
- Ambrosone CB, Nesline MK, Davis W: Establishing a Cancer Center Data Bank and Biorepository for multidisciplinary research, Cancer Epidemiol Biomarkers Prev 2006; 15(9):1575-7.
- Forman A, Jandorf L, Brown K, Rowse J, Moglia D, Farrell E, Carroll E, Kapil-Pair N, Valdimarsdottir H, Thompson H: Differing attitudes about genetic testing for BRCA1/2 in African American women compared to African Caribbean women. National Society of Genetic Counselors 25th Annual Education Conference. (2006)

- Rowse J, Brown K, Jandorf L, Forman A, Moglia D, Kapil-Pair N, Farrell E, Carroll E, Thompson H, Valdimarsdottir H: Breast cancer specific distress prior to genetic counseling in women of African descent at increased risk for hereditary breast and ovarian cancer. National Society of Genetic Counselors 25th Annual Education Conference. (2006)
- Dettenborn L, James GD, Valdimarsdottir HB, Montgomery GH, Bovbjerg DH: Elevated work-stress cortisol responses in women at familial risk for breast cancer: Predicted by intrusions about breast-cancer, J Psychophysiol 2006; 20(2):123-4.
- Gastrich HJ, Bovbjerg DH, James GD: Reproducibility of cortisol excretion patterns in women with and without familial risk of breast cancer, Am J Hum Biol 2006; 18(2):256-7.
- Forman A, Rowse J, Jandorf L, Brown K, Carroll E, Farrell E, Kapil-Pair N, Thompson H, Valdimarsdottir H: Predictors of distress in women of African descent at increased risk for an inherited breast cancer syndrome. National Society of Genetic Counselors 26th Annual Education Conference. (2007)
- Goldsmith R, Bovbjerg DH, Jandorf L, Valdimarsdottir HB, Amend KL, Ambrosone CB: Intrusive symptoms among women with breast cancer: the impact of childhood abuse. 10th European Conference on Traumatic Stress (2007)
- Farrell E, Rowse J, Forman A, Brown K, Jandorf L, Kapil-Pair N, Carroll E, Schwartz M, Thompson H, Bovbjerg D, Valdimarsdottir H: Racial disparities and cancer-specific distress among women seeking BRCA 1/2 counseling/testing. Society of Behavioral Medicine Annual Meeting & Scientific Sessions. (2007)
- Kapil-Pair N, Forman E, Carroll L, Jandorf L, Brown K, Rowse J, Moglia D, Farrell E, Schwartz M, Valdimarsdottir H, Thompson H: Differences in BRCA 1/2 testing attitudes between African Caribbean and African American women. 28th Annual Meeting & Scientific Sessions of the Society for Behavioral Medicine. (2007)
- Erwin DO, Johnson VA, Trevino M, Duke K, Feliciano L, Jandorf L: A comparison of African American and Latina social networks as indicators for culturally tailoring a breast and cervical cancer education intervention, Cancer 2007; 109(2):368-77.
- Gastrich HJ, van Berge-Landry H, Bovbjerg DH, James GD: Reproducibility of the difference in epinephrine response to work stress between women with and without a family history of breast cancer, Am J Hum Biol 2007; 19(2):256-7.
- Edwards TA, Forman A, Rowse J, Jandorf L, Brown K, Carroll E, Farrell E, Kapil-Pair N, Bovbjerg D, Thompson H, Valdimarsdottir H: Predictors of distress in women of African descent seeking genetic counseling: Personal history of cancer and death of first-degree relative from cancer, Ann Behav Med 2008; 35:S149.
- Sussner KM, Thompson HS, Jandorf L, Bovbjerg DH, Forman A, Schwartz MD, Valdimarsdottir HB: Perceived barriers to genetic testing for breast cancer among US and foreign-born black women, Psychooncology 2008; 17:S158.
- Edwards T, Thompson H, Kwate NO, Forman A, Kapil-Pair N, Jandorf L, Bovbjerg D, Valdimarsdottir H: Culture-specific coping as a mediator of optimism and psychological symptoms among women of African descent with a personal and/or family history of breast cancer, Psychooncology 2008; 17:S182-3.
- Sussner KM, Edwards TA, Thompson HS, Jandorf L, Kwate NO, Forman A, Kapil-Pair N., Brown K, Bovbjerg D, Schwartz, Valdimarsdottir H: Ethnic, racial and cultural

identity and perceptions about BRCA genetic testing among at-risk women of African descent. Society of Behavioral Medicine Annual Meeting & Scientific Sessions. (2010)

Training: Four postdoctoral fellows have participated in the training program during the course of the Center consistent with the SOW.

- DR. KEREN SHAKHAR received a PhD in Psychology from Tel Aviv University in Israel. Her research focused on neuroendocrine and immunological factors in breast cancer risk. After participating in the program Dr. Shakhar took a position as Tutor, Department of Psychology, Open University of Israel, Raanana, Israel.
  - Shakhar K, Valdimarsdottir HB, Bovbjerg DH: Heightened risk of breast cancer following pregnancy: Could lasting systemic immune alterations contribute? Cancer Epidemiol Biomarkers Prev 2007; 16(6):1082-6.
  - Shakhar K, Valdimarsdottir HB, Guevarra JS, Bovbjerg DH: Sleep, fatigue, and NK cell activity in healthy volunteers: significant relationships revealed by within subject analyses, Brain Behav Immun 2007; 21(2):180-4.
  - Shakhar K, Valdimarsdottir HB, Bovbjerg DH: Could lasting reductions in natural killer cell cytotoxic activity in women with older age of first full term pregnancy contribute to their increased risk of breast cancer? Annual Meeting of the American Psychosomatic Society. (2007)

- DR. CAROLINE WRIGHT received a PhD in Health Psychology from University College London in England. Her research centered on psychobiological reactivity. After participating in the program, she took a position as researcher with the Department of Health, United Kingdom.
  - Wright CE, Valdimarsdottir HB, Erblich J, Bovbjerg DH: Poor sleep the night before an experimental stress task is associated with reduced cortisol reactivity in healthy women, Biol Psychol 2007; 74(3):319-27.
  - Wright CE, Erblich J, Valdimarsdottir HB, Bovbjerg DH: Poor sleep the night before an experimental stressor predicts reduced NK cell mobilization and slowed recovery in healthy women, Brain Behav Immun 2007; 21(3);358-63.
  - Wright CE., Montgomery GM, Silverstein JH, Bovbjerg DH: Disrupted sleep the night before breast cancer surgery is associated with increased post-surgical pain. American Society of Clinical Oncology. (2007)
  - Wright CE, Montgomery GM, Silverstein JH, Bovbjerg DH: Disrupted sleep the night before breast cancer surgery is associated with increased post-surgical pain. Annual Meeting of the Society of Behavioral Medicine. (2007)
  - Wright CE, Valdimarsdottir HB, Erblich J, Bovbjerg DH: Poor sleep the night before and experimental stressor is associated with reduced cortisol reactivity in healthy women. Annual Meeting of the Society of Behavioral Medicine. (2007)
  - Wright CE, Montgomery GM, Silverstein JH, Bovbjerg DH: Disrupted sleep the night before breast cancer surgery is associated with increased post-surgical pain. Poster presentation at American Society of Clinical Oncology 43rd Annual Meeting. (2007)
  - Wright CE, Montgomery GM, Silverstein JH, Bovbjerg DH: Disrupted sleep the night before breast cancer surgery is associated with increased post-surgical pain.

Poster presentation at the Society of Behavioral Medicine 28th Annual Meeting. (2007) Nominated for Pain Special Interest Group annual student abstract award.
  - Wright CE, Valdimarsdottir HB, Erblich J, Bovbjerg H: Poor sleep the night before an acute experimental stressor is associated with reduced cortisol reactivity in healthy women. Paper and poster presentation at the Society of Behavioral Medicine 28th Annual Meeting. (2007)
  - Wright CE, Bovbjerg DH, Montgomery GH, Weltz C, Goldfarb A, Pace B, Silverstein JH: Disrupted sleep the night before breast surgery is associated with increased postoperative pain, J Pain Symptom Manage 2009; 37(3):352-62.

- DR. NAA OYO A. KWATE: Dr. Kwate received a PhD in Clinical Psychology from St. John's University in New York. Her research focused on health disparities in cancer prevention and control. After her participation in the program, Dr. Kwate became an Assistant Professor at the Mailman School of Public Health, Columbia University.
  - Kwate NOA: Intelligence or Misorientation?: Eurocentrism in the WISC-III. J Black Psychol 2001; 27(2): 221-38.
  - Kwate NOA: Re: Race, socioeconomic status, and breast cancer treatment and survival, J Natl Cancer Inst 2002; 94(16): 1254.
  - Kwate NOA: The projection of Eurocentrism in projective testing. In: African-centered Psychology: Culture-focusing for Multicultural Competence. Azibo DA (Ed). Durham, Carolina Academic Press, 2003.
  - Kwate NOA, Valdimarsdottir HB, Guevarra JS, Bovbjerg DH: Experiences of racist events are associated with negative health consequences for African American women. J Natl Med Assoc 2003; 95(6):450-60.
  - Kwate NOA: Cross-validation of the Africentrism Scale. J Black Psychol 2003; 29(3):308-324.
  - Thompson HS, Wahl E, Fatone A, Brown K, Kwate NOA, Valdimarsdottir H: Enhancing the readability of materials describing genetic risk for breast cancer, Cancer Control 2004; 11(4):245-53.
  - Bediako SM, Kwate NOA, Rucker R: Dietary behavior among African Americans: assessing cultural identity and health consciousness, Ethn Dis 2004; 14(4):527-32.
  - Utsey SO, Walker RL, Kwate NOA: Quantitative research in a multicultural context: Practical applications for research with ethnic minority populations. In: Strategies for Building Multicultural Competence in Mental Health and Educational Settings. Constantine M, Sue DW (Eds). New York, Jossey-Bass, 2005.
  - Guevarra JS, Kwate NO, Tang TS, Valdimarsdottir HB, Freeman HP, Bovbjerg DH: Acculturation and its relationship to smoking and breast self-examination frequency in African American women, J Behav Med 2005; 28(2):191-9.
  - Thompson HS, Kwate NOA: Genetic testing attitudes in the United States and Africa: The role of underdevelopment in perceived disadvantages and concerns about abuses. In: About Cancer in Africa. Paris: International Network Against Cancer in Africa.
  - Kwate NOA: The heresy of African-centered psychology, J Med Humanit 2005; 26(4):215-35.
  - Kwate NO, Thompson HS, Valdimarsdottir HB, Bovbjerg DH: Brief report: etiological attributions for breast cancer among healthy African American and European American women, Psychooncology 2005; 14(5):421-5.

- Kwate NO, Lee TH: Ghettoizing outdoor advertising: disadvantage and ad panel density in black neighborhoods, J Urban Health 2007; 84(1):21-31.
- Kwate NO, Jernigan M, Lee T: Prevalence, proximity and predictors of alcohol ads in Central Harlem, Alcohol Alcohol 2007; 42(6):635-40.
- Kwate NO: Take one down, pass it around, 98 alcohol ads on the wall: outdoor advertising in New York City's Black neighborhoods, Int J Epidemiol 2007; 36(5):988-90.
- Kwate NO: Fried chicken and fresh apples: Racial segregation as a fundamental cause of fast food density in black neighborhoods, Health Place 2008; 14(1):32-44.

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  - Thompson HS, Wahl E, Fatone A, Brown K, Kwate NOA, Valdimarsdottir H: Enhancing the readability of materials describing genetic risk for breast cancer, Cancer Control 2004; 11(4):245-53.
  - Jandorf L, Fatone A, Borker PV, Levin M, Esmond WA, Brenner B, Butts G, Redd WH: Creating alliances to improve cancer prevention and detection among urban medically underserved minority groups. The East Harlem Partnership for Cancer Awareness, Cancer 2006; 107(8 Suppl):2043-51.
  - Fatone AM, Moadel AB, Foley FW, Fleming M, Jandorf L: Urban voices: the quality-of-life experience among women of color with breast cancer, Palliat Support Care 2007; 5(2):115-25.
  - Fatone A, Jandorf L, Modibo Baker J, Brenner B, Butts G, Cornbill R, Itzkowitz SH, Levin M, Rothenberg A, Sacks H, Weeks M, Redd WH: East Harlem Partnership for Cancer Awareness (EHPCA): collaborative cancer screening and prevention research in an urban minority community. (submitted)

Conclusion

The results of this research have increased our understanding of the role of biobehavioral factors in interaction with genetic factors with regard to the heightened burden of breast cancer in African-American women. The interdisciplinary intellectual environment and tradition established by the Center (see Objectives) have had multiplicative effects not only on the research directly supported by the Center, but a wide range of related research efforts focused on important issues in breast cancer. As such the Center and the results to follow from the additional research engendered by this Center may thus have substantial implications for breast cancer prevention and control, as they may suggest novel strategies to reduce the threat posed by this disease to not only African-American women, but all women facing the threat of this disease. See detailed descriptions for each Project below.

References

1) Newman LA, Martin IK: Disparities in breast cancer, Curr Probl Cancer 2007; 31(3):134-56.

2) Demicheli R, Retsky MW, Hrushesky WJ, Baum M, Gukas ID, Jatoi I: Racial disparities in breast cancer outcome: insights into host-tumor interactions, Cancer 2007; 110(9):1880-8.
3) Morris GJ, Mitchell EP: Higher incidence of aggressive breast cancers in African American women: a review, J Natl Med Assoc 2008; 100(6):698-702.
4) Anderson WF, Rosenberg PS, Menashe I, Mitani A, Pfeiffer RM: Age-related crossover in breast cancer incidence rates between black and white ethnic groups, J Natl Cancer Inst 2008; 100(24):1804-14.
5) Gerend MA, Pai M: Social determinants of Black-White disparities in breast cancer mortality: a review, Cancer Epidemiol Biomarkers Prev 2008; 17(11):2913-23.
6) Albain KS, Unger JM, Crowley JJ, Coltman CA Jr, Hershman DL: Racial disparities in cancer survival among randomized clinical trials patients of the Southwest Oncology Group, J Natl Cancer Inst 2009; 101(14):984-92.
7) Vona-Davis L, Rose DP: The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review, J Womens Health (Larchmt) 2009; 18(6):883-93.
8) McKenzie F, Jeffreys M: Do lifestyle or social factors explain ethnic/racial inequalities in breast cancer survival?, Epidemiol Rev 2009; 31:52-66.
9) Antoni MH, Lutgendorf SK, Cole SW, Dhabhar FS, Sephton SE, McDonald PG, Stefanek M, Sood AK: The influence of bio-behavioral factors on tumour biology: pathways and mechanism, Nat Rev Cancer 2006; 6(3):240-8.
10) Mravec B, Gidron Y, Hulin I: Neurobiology of cancer: interactions between nervous, endocrine and immune systems as a base for monitoring and modulating the tumorigenesis by the brain, Semin Cancer Biol 2008; 18:150-63.
11) Thaker PH, Sood AK: Neuroendocrine influences on cancer biology, Semin Cancer Biol 2008; 18(3):164-70.
12) Stefanek ME, Andrykowski MA, Lerman C, Manne S, Glanz K; AACR Behavioral Science Task Force: Behavioral oncology and the war on cancer: partnering with biomedicine, Cancer Res 2009; 69(18):7151-6.
13) Armaiz-Pena GN, Lutgendorf SK, Cole SW, Sood AK: Neuroendocrine modulation of cancer progression, Brain Behav Immun 2009; 23(1):10-5.
14) Hankinson SE, Colditz GA, Willett WC: Towards an integrated model for breast cancer etiology: the lifelong interplay of genes, lifestyle, and hormones, Breast Cancer Res 2004; 6(5):213-8.
15) Metcalfe KA, Foulkes WD, Kim-Sing C, Ainsworth P, Rosen B, Armel S, Poll A, Eisen A, Gilchrist D, Chudley A, Ghadirian P, Maugard C, Lemire EG, Sun P, Narod SA: Family history as a predictor of uptake of cancer preventive procedures by women with a BRCA1 or BRCA2 mutation, Clin Genet 2008; 73(5):474-9.
16) Turnbull C, Rahman N: Genetic predisposition to breast cancer: past, present, and future, Annu Rev Genomics Hum Genet 2008; 9:321-45.
17) Howard AF, Balneaves LG, Bottorff JL: Women's decision making about risk-reducing strategies in the context of hereditary breast and ovarian cancer: a systematic review, J Genet Couns 2009; 18(6):578-97.
18) Forman AD, Hall MJ: Influence of race/ethnicity on genetic counseling and testing for hereditary breast and ovarian cancer, Breast J 2009; 15 Suppl 1:S56-62.
19) Gregg G: Psychosocial issues facing African and African American women diagnosed with breast cancer, Soc Work Public Health 2009; 24(1-2):100-16.

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Appendices

<u>Manuscripts:</u>

Edwards TA, Thompson HS, Kwate NO, Brown K, McGovern MM, Forman A, Kapil-Pair N, Jandorf L, Bovbjerg DH, Valdimarsdottir HB: Association between temporal orientation and attitudes about BRCA1/2 testing among women of African descent with family histories of breast cancer, Patient Educ Couns 2008; 72(2):276-82. PMC2703430

Sussner KM, Thompson HS, Jandorf L, Edwards TA, Forman A, Brown K, Kapil-Pair N, Bovbjerg DH, Schwartz MD, Valdimarsdottir HB: The influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing for breast cancer among women of African descent, Psychooncology 2009; 18(9):945-55. PMC2735601

Fejerman L, Haiman CA, Reich D, Tandon A, Deo RC, John EM, Ingles SA, Ambrosone CB, Bovbjerg DH, Jandorf LH, Davis W, Ciupak G, Whittemore AS, Press MF, Ursin G, Bernstein L, Huntsman S, Henderson BE, Ziv E, Freedman ML: An admixture scan in 1,484 African-American women with breast cancer, Cancer Epidemiol Biomarkers Prev 2009; 18:3110-7. PMC2783219

Goldsmith RE, Jandorf L, Valdimarsdottir H, Amend KL, Stoudt BG, Rini C, Hershman D, Neugut A, Reilly JJ, Tartter PI, Feldman SM, Ambrosone CB, Bovbjerg DH: Traumatic stress symptoms and breast cancer: the role of childhood abuse, Child Abuse Negl 2010; 34(6):465-70. PMID: 20400179

Ambrosone CB, Ciupak GL, Bandera EV, Jandorf L, Bovbjerg DH, Zirpoli G, Pawlish K, Godbold J, Furberg H, Fatone A, Valdimarsdottir H, Yao S, Li Yulin, Hwang H, Davis W, Roberts M, Sucheston L, Demissie K, Amend KL, Tartter P, Reilly J, Pace BW, Rohan T, Sparano J, Raptis G, Castaldi M, Estabrook A, Feldman S, Weltz C, Kemeney M: Conducting molecular epidemiological research in the age of HIPAA: A multi-institutional case-control study of breast cancer in African-American and European-American women, J Oncology; EPub 2009 Oct 25. *In press* PMC2766507

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Association between temporal orientation and attitudes about *BRCA*1/2 testing among women of African descent with family histories of breast cancer

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Abstract

Objective: Previous studies have identified specific attitudes (pros and cons) about *BRCA* testing held by women of African descent that are associated with decisions to participate in testing. These testing attitudes may be determined, in part, by temporal orientation, or how one perceives the significance of events and the consequences of their actions in terms of past, present, and future. The current study explored the relationship between temporal orientation and pros and cons of *BRCA* testing among 140 women of African descent with a family history suggestive of a genetic mutation predisposing to breast cancer.

Methods: Participants completed measures of temporal orientation and genetic testing attitudes.

Results: Multivariate analyses indicated that future orientation was positively associated with perceived pros of testing. Additional analyses revealed significant associations between temporal orientation and specific item subsets related to the negative and positive impact of testing on family and personal control over one's health.

Conclusion: These results support an association between temporal orientation and attitudes about *BRCA* testing among women of African descent with family histories of breast cancer.

Practice implications: Findings support exploration of temporal orientation in future research on *BRCA* testing decisions among women of African descent and this construct's importance in developing decision aids and tailoring genetic counseling.

Keywords: Cancer; Breast cancer; BRCA1/2 testing; Black women; Temporal orientation; Health attitudes

1. Introduction

Approximately 5–10% of newly diagnosed breast cancer cases are due to deleterious mutations in the *BRCA*1 and *BRCA*2 genes [1]. Estimates suggest that individuals with these gene alterations have up to an 85% lifetime risk of developing breast cancer and up to a 60% lifetime risk of developing ovarian cancer [2,3]. The availability of genetic counseling and testing for breast and ovarian cancer susceptibility has increased in recent years and may provide individuals with cancer risk information which may affect screening and treatment decisions. Interestingly, research has found that although women of African descent at high risk for having a *BRCA* mutation report a high level of interest and intention to participate in genetic counseling and testing [4], participation rates remain lower relative to white women [2].

Some authors argue that participation rates may be related to attitudes about *BRCA* testing, including perceived advantages (pros) and disadvantages (cons). A number of studies report that women of African descent report more favorable attitudes concerning the benefits of genetic testing, relative to white women, including, the potential prevention of cancer, reduction of uncertainty, reassurance, and the ability to make informed

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cancer screening and treatment decisions [5,6]. However, genetic testing has also been found to provoke a number of concerns for women of African descent, including concerns about confidentiality and anticipation of negative emotional reactions [5], concern for family members [6], and concerns about the potential for abuse of testing results [7]. For all of these findings, racial differences remained even when controlling for socioeconomic status.

There is a growing body of research focusing on the social and cultural context of *BRCA* testing attitudes endorsed by women of African descent. Several researchers have noted that certain worldviews and cultural factors, such as communalism, religion, spirituality, and temporal orientation may influence perceived advantages and disadvantages of cancer prevention and control behaviors, including interest and participation in genetic testing [3]. Of these factors, ‘‘temporal orientation or how one perceives the significance of events and the consequences of their actions in terms of past, present, and future implications’’ ([3], p. 108), has been shown to have significant influence on health-related decision making [8].

A number of researchers have asserted that temporal orientation is associated with worldview and cultural values. For example, Graham [9] describes the Anglo cultural perception of time as linear and able to be separated into distinct parts – past, present, and future – where the future represents a new and different set of situations for which one can prepare. He posits that in non-Anglo cultures, time is perceived to be more circular as opposed to linear; experiences are cyclical; and people expect a future that is much like the past. Thus, a focus on the needs and concerns of the present is more practical than a focus on the future. Jones [10] argues a similar point by suggesting that institutional racism encountered by those growing up Black in the U.S. has served to provide disconfirming evidence that one has any direct influence on future outcomes. As a result, some African Americans may be less future-oriented and more present-oriented. The notion that a present orientation may be more salient in African American culture is supported by the findings of one study which found that African Americans were more present-oriented than White Americans in relation to their daily experiences with managing hypertension [8].

In a recent review of the literature on the relationship between preventive health behaviors and temporal orientation, Chapman [11] suggests that one explanation for many individuals’ non-adherence to cancer prevention and control behaviors is that they are present-oriented and place greater value on immediate costs or disadvantages of these behaviors and less value on their future benefits (p. S41). For example, a woman who is more present-oriented may focus on the immediate costs of having a mammogram, such as time away from work, the inconvenience of re-scheduling responsibilities, or anticipated discomfort. Less attention is paid to the benefits of mammography that are often delayed, such as earlier detection of cancer that may lead to improved treatment and survival outcomes. For a woman who is present-oriented, the costs may be perceived as too great and may lead her to delay or even avoid screening altogether, particularly in the absence of symptoms. Thus, understanding the value that an individual places on immediate costs versus delayed benefits of cancer control behaviors is imperative in understanding participation, or lack thereof, in these behaviors.

BRCA testing attitudes may be similarly informed by temporal orientation to the extent that many of the benefits of genetic testing, such as its influence on breast cancer screening decisions over time, are also delayed. Therefore, individual’s who are more present-oriented may be less likely to recognize the benefits of testing; thus, less likely to participate. Researchers have begun to examine temporal orientation and its association to *BRCA* genetic testing decisions. In a recent study, Levy et al. [12] found that future time orientation was significantly higher in women who participated in genetic counseling for *BRCA*1/2 testing. The authors discussed how a behavior like counseling for predictive genetic testing, which they described as being explicitly related to future risk, would more likely be associated with future orientation. Similarly, Hughes and colleagues [3] reported that among women of African descent at high risk for a *BRCA*1/2 gene alteration, future orientation was higher among test acceptors relative to test decliners. These authors noted that temporal orientation likely influences the perception of advantages and disadvantages of genetic testing. Levy et al. [12] further suggested ‘‘. . . a person who places high value on the present (compared to the future) will perceive relatively lower benefits from preventive health behavior than a person who places a relatively high value on the future. . .’’ (p. 955). Conversely, those who place a high value on the future may be expected to perceive greater benefits from preventive health behavior. Although the aforementioned authors were able to show that a relationship does exist between temporal orientation and genetic counseling and test acceptance, no studies to date have explored the association between temporal orientation and perceived genetic testing attitudes, which the authors argue likely influence counseling and test participation decisions. The current study will attempt to further tease apart the assumptions made by Levy et al. [12], by examining this association.

Therefore, the current study aims to explore the association between temporal orientation and *BRCA* testing attitudes in a sample of women of African descent with a family history suggestive of a genetic mutation predisposing to breast cancer. Exploration of this association within this group is important as temporal orientation may be a culturally salient factor likely influencing testing attitudes. Based upon prior research with similar populations, we hypothesize that future orientation will be associated with greater endorsement of perceived pros of *BRCA* testing and lower endorsement of perceived cons, while present orientation will be associated with greater endorsement of perceived cons of *BRCA* testing and lower endorsement of perceived pros.

2. Methods

2.1. Participants

Participants were 140 women of African descent with a personal and/or family history suggestive of a hereditary cancer syndrome. Family history eligibility criteria was assessed using standard *BRCA1/2* risk probability models, namely, the Myriad Model, Penn Model, and BRCApro [13–15]. Participants whose family histories suggested that the cancer in their family might be inherited based upon *any* of these models were recruited for participation into the study. Among the sample, 39% had 1 relative; 38% had 2 relatives; and 23% had 3 or more relatives affected with breast or ovarian cancer. Women were considered ineligible if they were under the age of 18, non-English speaking, pregnant, unable to provide informed consent, or had previously undergone genetic counseling for hereditary breast/ovarian cancer. Eligible participants were offered genetic counseling and testing at no charge.

2.2. Procedure

This study is part of a larger longitudinal program of research evaluating the impact of standard genetic counseling (SGC) versus culturally tailored genetic counseling (CT-GC) on *BRCA*1/2 decision making and psychobehavioral outcomes. The present study utilized a community based recruitment effort, relying largely upon physician referral and participant initiation. The majority of participants in the sample were recruited following women's initiation of contact with the study team based on physician referral or community outreach. Therefore, the total number of women referred to the study is unknown. Of the 154 eligible women who contacted the study team, 14 declined participation.

Eligible participants were first scheduled for a baseline telephone interview. All interviews were conducted by telephone by trained research assistants from Mount Sinai School of Medicine, Department of Genetics and Genomic Sciences. Consent forms were mailed to those women interested in participation and a baseline interview was scheduled. During the baseline interview, questions related to demographic and medical characteristics, time orientation, and *BRCA* testing attitudes were included. Colored answer key cards were mailed to participants to assist in answering the questionnaires over the telephone. Following completion of the baseline interview, participants were given the option of pursuing genetic counseling and testing for *BRCA1* and *BRCA2*. All study procedures and documents were approved by the Mount Sinai School of Medicine Institutional Review Board. For our purposes, we focused solely on information obtained during the baseline telephone interview pertaining to temporal orientation and *BRCA* testing attitudes.

2.3. Measures

2.3.1. Sociodemographic and medical information

Basic sociodemographic and medical information was obtained from each participant, including age, marital status, education, income, health insurance coverage, and breast cancer history.

2.3.2. Temporal orientation

A previously validated scale [16] was used to assess individual's tendency to think and act according to consequences that are primarily present (e.g., ''There's no sense in thinking about the future before it gets here'') or future oriented (e.g., ''I often think about how my actions today will affect my health when I am older''). The scale consists of 10-items, which are divided into two, 5-item subscales, one measuring present and the other measuring future time orientation (possible range: 5–20). Participants indicated the extent to which they agreed or disagreed with each item using a Likert scale ranging from 1 (strongly agree) to 4 (strongly disagree). The internal consistency for the present ($\alpha = .62$) and future scales ($\alpha = .67$) were moderate.

2.3.3. Genetic testing pros and cons

This 23-item measure was developed by the research team to assess perceived pros and cons of genetic testing for breast cancer susceptibility. Items were based on our previous research [17,7], as well as that of others [6,18,19]. Participants indicated the extent to which they agreed or disagreed with each question using a Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree). Nine items ($\alpha = .76$) assessed the pros of genetic testing (possible range: 9–45) and 14 items ($\alpha = .81$) assessed the cons of testing (possible range: 14–70). The pro scale included three subsets: (1) surveillance behaviors (e.g., ''Knowing that I carry the gene mutation would motivate me to perform breast self-examination more frequently''); (2) family related pros (e.g., ''My genetic test results could give my family members useful information about their risk of getting cancer''); and (3) personal control (e.g., Knowing whether I had the gene mutation would increase my sense of personal control); while the con scale included four subsets: (1) anticipation of negative emotional reaction (e.g., ''Knowing that I carry the gene mutation would leave me in a state of hopelessness and despair''); (2) confidentiality concerns (e.g., ''If I were found to carry the gene mutation, I would worry that the results would not stay confidential''); (3) stigma related to testing (e.g., ''If I were found to carry a gene mutation for cancer, it would cause others to view me negatively''); and (4) family related cons (e.g., ''If I underwent genetic testing for cancer, I would be concerned about the effect it would have on my family''). The internal consistencies of each of the seven subsets of items in the current sample are as follows: surveillance behaviors ($\alpha = .72$); family related pros ($\alpha = .84$); negative emotional reaction ($\alpha = .69$); confidentiality concerns ($\alpha = .70$); stigma related to testing ($\alpha = .73$); family related cons ($\alpha = .65$); and personal control ($\alpha = .66$).

3. Results

3.1. Demographic characteristics

As shown in Table 1, participants included a wide age range, with a mean age of 45.6 years. A little over half of the participants reported greater than $35,000 in annual income, two-thirds reported greater than a high school education (some college, college graduate, or post-graduate degree), one-third of the participants were married, and a little over three-quarters of the participants reported some form of medical insurance. Of

Table 1
Participant characteristics ($N = 140$)

Variable	n (%)
Age, mean (range) (year)	45.6 (22–79)
Race/ethnicity	
Black-African American	74 (56%)
Black-West Indian/Caribbean	58 (44%)
Marital status	
Single	49 (35%)
Married	44 (31%)
Divorced/separated	41 (30%)
Widowed	6 (4%)
Education	
Less than 8th grade	2 (1%)
8th to 11th grade	8 (6%)
High school graduate or equivalent	35 (25%)
Technical or vocational school	7 (5%)
Some college	44 (31%)
College graduate	29 (21%)
Post-graduate degree	15 (11%)
Annual household income	
<$15,000	25 (19%)
$15,000–24,999	18 (13%)
$25,000–34,999	14 (10%)
$35,000–49,999	22 (16%)
$50,000–69,999	22 (16%)
$70,000–89,999	12 (9%)
>$90,000	13 (10%)
Health insurance	
Insured	120 (86%)
Uninsured	20 (14%)
Personal breast cancer history	
Affected	94 (69%)
Unaffected	42 (31%)

the participants in the present study, a little over half of the women were African American while the remainder self-identified as African Caribbean. Among the participants in this study, greater than half reported a personal history of breast cancer. Of those affected, the mean age of onset was 43.4 years.

3.2. Genetic testing pros and cons

Endorsements of perceived pros and cons were descriptively analyzed by tabulating the percentages of women who agreed or strongly agreed with each of the pros (Table 2) and cons (Table 3). A majority of women (>80%) reported agreement with 6 of the 9 pro items, with the remaining three items receiving agreement from greater than half of the women. Three of the 14 con items, all of which addressed effects of testing on family, received >50% agreement among the women.

3.3. Temporal orientation and demographic characteristics

Among the demographic characteristics, age was found to be significantly associated with temporal orientation. Older age was found to be associated with present-orientation, whereas younger age was associated with future-orientation

Table 2
Perceived pros of genetic testing

Perceived pro items	Agree or strongly agree (%)
Family related pros	
If I were found to carry the gene mutation, it would help my daughter(s) or sister(s) decide whether to undergo genetic testing	92
My genetic test results could give my family members useful information about their risk of getting cancer	97
My genetic test results could help my family members make better decisions about how to take care of their health	95
Genetic testing would help me learn if my children were at risk for getting breast cancer.	91
Surveillance behaviors	
Knowing that I carry the gene mutation would motivate me to perform breast self-examination more frequently	91
Knowing that I carry the gene mutation would help me decide whether to go for more frequent mammograms	83
Personal control	
My concerns about getting breast cancer again would be reduced if I knew I did not carry the gene mutation	74
Knowing whether I had the gene mutation would increase my sense of personal control	76
Knowing whether I have the gene mutation or not would help me make important life decisions (e.g., getting married, having children)	70

($r = .26$, $p = .002$ and $r = -.20$, $p = .02$, respectively). An ANOVA revealed a significant association between personal history and temporal orientation. Women with a personal history of breast cancer had higher present-orientation scores compared to those women without a personal history ($F(1,135) = 11.84$, $p = .001$). There were no significant associations found between demographic characteristics and pro and con total scores.

3.4. Temporal orientation and genetic testing pros and cons

Simultaneous multiple regression was used to assess the association between temporal orientation and pro and con total scores while adjusting for age and personal history of breast cancer. As can be seen in Table 4, results revealed a significant association for future orientation. Consistent with our hypothesis, future orientation was positively related to the pro total score ($\beta = .271$, S.E. = .09, $p = .002$). Interestingly, neither future nor present orientation was significantly related to the con total score as hypothesized.

Additional analyses were performed at the item subset level to determine which subsets were related to present and future orientation. Results of these adjusted analyses revealed that present orientation was negatively associated with family related pros ($\beta = -.223$, S.E. = .11, $p = .05$) and personal

Table 3
Perceived cons of genetic testing

Perceived con items	Agree or strongly agree (%)
Family related cons	
If I underwent genetic testing for cancer, I would be concerned about the effect it would have on my family	52
If I were found to carry the gene mutation for breast cancer, I would worry about passing the gene to my children	75
Knowing that I carry the gene mutation would cause me to worry more about other family members who could be carriers (e.g., mother, sisters, daughters)	72
If I were found to carry the gene for breast cancer, I would feel guilty if my daughter(s) developed breast cancer	29
I would feel guilty if one of my relatives had the gene mutation and I did not	11
Stigma related to testing	
If I were found to carry a gene mutation for cancer, I would feel singled out	8
If I were found to carry a gene mutation for cancer, it would cause others to view me negatively	3
I would be ashamed if I were found to carry the gene mutation	2
Anticipation of negative emotional reaction	
I would be frightened if I were found to carry the gene mutation	37
Knowing that I carry the gene mutation would leave me in a state of hopelessness and despair	2
I would consider suicide if I were found to carry the gene mutation for breast cancer	0
If I underwent genetic testing for cancer, I would not be able to handle it emotionally	3
Confidentiality concerns	
If I were found to carry the gene mutation, I would worry that the results would not stay confidential	12
Being tested for the gene mutation could jeopardize my insurance coverage	11

control ($\beta = -.318$, S.E. = .16, $p = .05$). Future orientation was found to be positively associated with family related pros ($\beta = .263$, S.E. = .10, $p = .01$), family related cons ($\beta = .240$, S.E. = .12, $p = .05$), and personal control ($\beta = .329$, S.E. = .14, $p = .02$).

Table 4
Summary of regression analyses

Variable	S.E. *B*	β	Significance
Present orientation			
Family related pros	.11	−.223	.05
Personal control	.16	−.318	.05
Future orientation			
Pro total score	.09	.271	.002
Family related pros	.10	.263	.01
Personal control	.14	.329	.02
Family related cons	.12	.240	.05

4. Discussion and conclusion

4.1. Discussion

In the current study, findings support an association between temporal orientation and attitudes about *BRCA* testing in a sample of women of African descent with family histories of breast cancer. As expected, future orientation was associated with greater endorsement of overall testing advantages. This result extends the work of others in the area [3,12], who have found future orientation to be higher in genetic counseling and testing acceptors, but have not explored potential mediators of this association.

Additional analyses revealed that present and future orientation were related to both pro and con item subsets. The positive relationship found between future orientation and family related pros of testing suggests that for women who tend to think and act according to more future consequences, the extent to which *BRCA* testing results provide useful information related to family members' future cancer risk was viewed as beneficial. The vast majority of women (95%) agreed that testing could help family members make better decisions about health care and an even greater number (97%) agreed that test results could provide family members with useful information about their own risk. This finding is consistent with previous studies, which found that 89–91% ([17,4]; respectively) of participants indicated that genetic testing would help family members make more informed testing-related decisions. Previous research has indicated that future oriented individuals are more inclined to participate in genetic counseling and testing, and being that the nature of testing is to provide both personal and familial risk information, it is not surprising that family benefits is a potential mediator between time orientation and genetic testing.

Contrary to expectations, future orientation was found to be positively associated with family related cons of testing, including feelings of guilt and worry about family members' carrier status and concern about the effect of testing on family. It could be speculated that the family members these women are most concerned about are children for whom these consequences may not be relevant or apparent for a number of years. For a woman who is future-oriented, the potentially negative future impact of BRCA test results on the children in her family may be viewed as a considerable disadvantage of testing. These attitudes may be further compounded within this population by a strong sense of collectivism and familial interdependence that has been noted as salient in African American culture and has been cited by several researchers as a factor influencing BRCA testing decisions [3,17].

Future orientation was found to be positively associated with perceived personal control, suggesting that for women who tend to think and act according to more future consequences, the extent to which *BRCA* testing would increase their sense of personal control and ability to make appropriate decisions concerning the management of cancer risk was viewed as an incentive to participate in genetic testing. A fair percentage of the women (76%) reported that testing would help to increase their sense of personal control and a similar number (70%) believed that testing would aid in making important life decisions. These findings are not surprising and reflect similar results found in other studies, where 67–74% believed that testing would increase their sense of personal control and 70–74% believed testing would help in making important life decisions [17,4]. Although this is the first study to show a relationship between temporal orientation and perceived personal control in relation to cancer prevention and management, other researchers have found that among women of African descent at increased risk, ‘the need to plan for the future’ [20] and ‘taking certain steps to prevent cancer’ [6,21] are rated as important factors affecting decisions to participate in genetic counseling and testing. In addition, one can speculate that for future oriented women, the belief that the information received from genetic testing can help in making major future life decisions and increase one’s sense of personal control, would be perceived as beneficial.

In contrast, present orientation was negatively associated with personal control, suggesting that for women who tend to think and act according to more immediate consequences, the perceived benefits that testing could provide in terms of strengthening one’s sense of personal control were not viewed as advantageous. It is plausible to assume that women who are more present oriented focus on more immediate concerns that may effect their ongoing personal and social experiences. Therefore, the immediate consequences of genetic testing participation and receipt of results, may not be viewed as aiding in reducing concerns regarding breast cancer, but may be viewed instead as one more thing to be concerned about and needing to be dealt with in the here and now. This assumption may also explain the expected relationship found between present orientation and family related pros of testing.

Interestingly, the present study found no significant differences between African American and Caribbean women regarding genetic testing attitudes or temporal orientation. To date, no studies have described within group differences among women of African descent with regard to the relationship between temporal orientation and genetic testing attitudes. The lack of significant temporal orientation differences may be attributed to the aforementioned model described by Graham [9] as the ‘circular-traditional’ perception of time, which has been observed in non-Western cultures. As African Americans and African Caribbeans share common African ancestry, the absence of differences between these groups regarding this culturally relevant construct may reflect retention of this shared ancestry. The absence of differences may also be attributed to beliefs about perceived low control over future outcomes due to comparable histories of oppression: racism in the United States and foreign colonialism in Caribbean nations. Future work should examine the extent to which differences exist or are absent between the two groups among other culturally relevant constructs.

4.2. Conclusion

These findings support an association between present and future orientation and attitudes about *BRCA* testing in a sample of women of African descent with family histories of breast cancer.

4.3. Practice implications

The present findings, demonstrating a relationship between temporal orientation and attitudes about genetic testing have a number of practice implications and should be of particular interest to health care providers and researchers interested in issues relevant to *BRCA* testing. First, these results add to the current body of literature on potential culturally relevant factors that may serve to influence *BRCA* testing attitudes and, ultimately, *BRCA* testing participation decisions among women of African descent. Given the growing focus on culturally competent health care, including the provision of genetic risk assessment services, awareness of temporal orientation as a factor in women’s testing decisions may help to increase genetic counselors’ sensitivity to the sociocultural context within which women make such decisions. Similarly, structured decision aids designed to facilitate genetic testing decisions could also be potentially strengthened by taking into account the sociocultural context within which women may make testing-related decisions.

Similar to health care professionals’ efforts to educate diverse populations about cancer prevention related behaviors, such as mammography or colonoscopy, genetic counselors’ efforts to impart information related to *BRCA* testing may integrate temporal orientation into their approaches for women of African descent. This may include the development and presentation of messages and materials that acknowledge variability in present and future orientation across women and the impact it has on health-related behaviors and decisions. Given the considerable resources allocated to increasing screening participation among African Americans, who have the highest cancer mortality rates across a number of cancer types, as well as the growing focus on culturally targeted and tailored interventions (see [22,23]; for review on tailoring), continued exploration of the influence of temporal orientation is warranted in both research and intervention design.

4.4. Limitations

Several limitations of the present study must be acknowledged. First, the generalizability of the results may be somewhat limited, as our sample was fairly homogenous, consisting of middle-class educated women of African descent. According to the U.S Census Bureau, based on data from the 2004 American Community Survey [24], about 26% of African Americans live below the poverty line and roughly 17% of Black women have a bachelor’s degree or more education, compared to the current sample in which 51% of the participants reported equal to or greater than $35,000 in annual income and 32% reported receipt of bachelor’s degree or more education. Thus, the present sample of women may not be representative of the larger population of women of African descent, particularly in terms of income and education. Second, an additional limitation of the present study is the modest internal consistencies of the present and future orientation subscales, which is likely due to the low number of items within each subscale. Internal consistencies for the original study [16] also revealed moderate alphas (.73 and .72 for present and future, respectively). However, the expected relationships found between temporal orientation and other study variables provide some evidence of the stability of the measure. A similar explanation is warranted for the low internal consistency coefficients found for several of the genetic testing pro and con subscales. Future development of additional items for these subscales and evaluation within a larger sample may aid in strengthening the reliability of these subscales and the larger scale overall. Third, as aforementioned, the participants in this sample were recruited following women's initiation of contact with the study team based on physician referral or community outreach. Some of these women may have contacted the study team because they had an existing interest in obtaining *BRCA* counseling and testing. Furthermore, the counseling and testing offered free of charge, to all women, through study participation may have provided an additional incentive. It is plausible that these women may have entered the study with relatively positive attitudes toward *BRCA* testing, thus biasing the responses of the sample overall. However, 5 of the 14 con items were endorsed by one-third or more of the entire sample suggesting that attitudes were not uniformly positive. Still, this remains an important methodological issue that has been discussed in similar studies [25,18] and warrants future research to develop strategies to address these issues. Lastly, although the present study addresses an important theoretical issue, future work can extend these findings by exploring the uptake of genetic counseling and testing as behavioral outcomes.

References

[1] National Cancer Institute. Genetic Testing for BRCA1 and BRCA2: it's your choice. 2002. Retrieved January 28, 2008, from http://www.cancer.gov/cancertopics/factsheet/Risk/BRCA.

[2] Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of *BRCA*1/2 testing among women with a family history of breast or ovarian cancer. J Am Med Assoc 2005;293:1729–36.

[3] Hughes C, Fasaye G, LaSalle VH, Finch C. Sociocultural influences on participation in genetic risk assessment and testing among African American women. Patient Educ Couns 2003;51:107–14.

[4] Kinney AY, Croyle RT, Dudley WN, Bailey CA, Pelias MK, Neuhausen SL. Knowledge, attitudes, and interest in breast–ovarian cancer gene testing: a survey of a large African American kindred with a *BRCA*1 mutation. Prev Med 2001;33:543–51.

[5] Donovan KA, Tucker DC. Knowledge about genetic risk for breast cancer and perceptions of genetic testing in a sociodemographically diverse sample. J Behav Med 2000;23:15–36.

[6] Hughes C, Gomez-Caminero A, Benkendorf J, Kerner J, Isaacs C, Barter J, Lerman C. Ethnic differences in knowledge and attitudes about *BRCA*1 testing in women at increased risk. Patient Educ Couns 1997;32:51–62.

[7] Thompson HS, Valdimarsdottir HB, Jandorf L, Redd W. Perceived disadvantages and concerns about abuses of genetic testing for cancer risk: differences across African American, Latina, and Caucasian women. Patient Educ Couns 2003;51:217–27.

[8] Brown CM, Segal R. Ethnic differences in temporal orientation and its implications for hypertension management. J Health Soc Behav 1996;37: 350–61.

[9] Graham RJ. The role of perception of time in consumer research. J Consum Res 1981;7:335–42.

[10] Jones JM. Cultural differences in temporal orientation: instrumental and expressive behaviors in time. In: McGrath JE, editor. The social psychology of time: new perspectives. Newbury Park, CA: Sage; 1988. p. 21–37.

[11] Chapman GB. Short-term cost for long-term benefit: time preference and cancer control. Health Psychol 2005;24:S41–8.

[12] Levy AG, Micco E, Putt M, Armstrong K. Value for the future and breast cancer-preventive health behavior. Cancer Epidemiol Biomarkers Prev 2006;15:955–60.

[13] Parmigiani G, Berry DA, Aquilar O. Determining carrier probabilities for breast cancer susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 1998;62:145–58.

[14] Couch FJ, DeShano ML, Blackwood MA, Calzone K, Stopfer J, Campeau L, Ganguly A, Rebbeck T, Weber BL, Jablon L, Cobleigh MA, Hoskins K, Garber JE. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. N Eng J Med 1997;336:1409–15.

[15] Frank TS, Manley SA, Olopade OI, Cummings S, Garber JE, Bernhardt B, Antman K, Russo D, Wood ME, Mullineau L, Isaacs C, Peshkin B, Buys S, Venne V, Rowley PT, Loader S, Offit K, Robson M, Hampel H, Brener D, Winer EP, Clark S, Weber B, Strong LC, Rieger P, McClure M, Ward BE, Shattuck-Eidens D, Oliphant A, Skolnick MH, Thomas A. Sequence analysis of BRCA1 and BRCA2: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol 1998;16:2417–25.

[16] Lukwago SN, Kreuter MW, Bucholtz DC, Holt CL, Clark EM. Development and validation of brief scales to measure collectivism, religiosity, racial pride, and time orientation in urban African American women. Fam Community Health 2001;24:63–71.

[17] Thompson HS, Valdimarsdottir HB, Duteau-Buck C, Guevarra J, Bovbjerg DH, Richmond-Avellaneda C, Amarel D, Godfrey D, Brown K, Offit K. Psychosocial predictors of *BRCA* counseling and testing decisions among urban African-American women. Cancer Epidemiol Biomarkers Prev 2002;11:1579–85.

[18] Jacobsen PB, Valdimarsdottir HB, Brown KL, Offit K. Decision-making about genetic testing among women at familial risk for breast cancer. Psychosom Med 1997;59:459–66.

[19] Lerman C, Narod S, Schulman K, Hughes C, Gomez-Caminero A, Bonney G, Gold K, Trock B, Main D, Lynch J, Fulmore C, Snyder C, Lemon SJ, Conway T, Tonin P, Lenoir G, Lynch H. *BRCA*1 testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes. J Am Med Assoc 1996;275:1885–929.

[20] Matthews AK, Cummings S, Thompson S, Wohl V, List M, Olopade OI. Genetic testing of African Americans for susceptibility to inherited cancers: use of focus groups to determine factors contributing to participation. Psycho-oncology 2000;18:1–19.

[21] Kessler L, Collier A, Brewster K, Smith C, Weathers B, Wileyto EP, Halbert CH. Attitudes about genetic testing and genetic testing intentions in African American women at increased risk for hereditary breast cancer. Genet Med 2005;7:230–8.

[22] Kreuter M, Strecher V, Glassman B. One size does not fit all: the case for tailoring print materials. Ann Behav Med 1999;21:1–9.

[23] Kreuter MW, Lukwago SN, Bucholtz DC, Clark EM, Sanders-Thompson V. Achieving cultural appropriateness in health promotion programs: targeted and tailored approaches. Health Educ Behav 2002;30: 133–46.

[24] U.S. Census Bureau Website, available at http://www.census.gov/prod/2007pubs/acs-04.pdf. Accessed August 15, 2007.

[25] Durfy SJ, Bowen DJ, McTiernan A, Sporleder J, Burke W. Attitudes and interest in genetic testing for breast and ovarian cancer susceptibility in diverse groups of women in western Washington. Cancer Epidemiol Biomarkers Prev 1999;8:369–75.

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The influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing for breast cancer among women of African descent

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Abstract

Objective—Rising health disparities are increasingly evident in relation to use of genetic services (including genetic counseling and testing) for breast cancer risk, with women of African descent less likely to use genetic services compared with Whites. Meanwhile, little is known regarding potential within-group acculturation and psychological differences underlying perceived barriers to genetic testing among women of African descent.

Methods—Hypothesized contributions of acculturation factors and breast cancer-specific distress to perceived barriers to genetic testing were examined with a statistical analysis of baseline data from 146 women of African descent (56% US born and 44% foreign born) meeting genetic breast cancer risk criteria and participating in a larger longitudinal study that included the opportunity for free genetic counseling and testing. Perceived barriers assessed included: (1) anticipation of negative emotional reactions, (2) stigma, (3) confidentiality concerns, (4) family-related worry, and (5) family-related guilt associated with genetic testing.

Results—In multivariate analyses, being foreign born was a significant predictor of anticipated negative emotional reactions about genetic testing (β= 0.26; SE=0.11; $p = 0.01$). Breast cancer-specific distress scores (avoidance symptoms) were positively related to anticipated negative emotional reactions ($\beta = 0.02$; SE= 0.005; $p = <0.0001$), confidentiality concerns ($\beta = 0.02$; SE = 0.01; $p = 0.02$), and family-related guilt ($\beta = 0.02$; SE=0.01; $p = 0.0009$) associated with genetic testing.

Conclusions—Results suggest an influence of acculturation and breast cancer-specific distress on perceived barriers to genetic testing among women of African descent. The potential utility of culturally tailored genetic counseling services taking into account such influences and addressing

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emotional and psychological concerns of women considering genetic testing for breast cancer should be investigated.

Keywords

cancer; oncology; genetic testing; breast; African

Introduction

Women with a mutation in one of the major breast cancer susceptibility genes *BRCA1 or BRCA2* have a 40–66% lifetime risk of developing breast cancer, as well as a 13–46% risk of developing ovarian cancer, and if they have already been diagnosed with breast cancer in one breast they have up to a 52% risk of developing cancer in their other breast [1,2]. Genetic services for breast cancer (including genetic counseling and testing) allow women with family histories of the disease an opportunity to make more informed decisions regarding cancer prevention options, including risk reducing surgery, chemoprevention, and surveillance/ screening [3,4]. Yet, despite the growing use of genetic services for breast cancer in recent years, research documents rising racial disparities in the use of such services [5,6]. White women are almost five times more likely to undergo genetic counseling for *BRCA1/2* testing compared with women of African descent, controlling for other factors [7]. Such disparities are particularly alarming as studies suggest that between 16 and 28% of women of African descent with personal or family history of breast and/or ovarian cancer may carry *BRCA1/2* mutations [8–11]. Further, despite a lower breast cancer incidence rate, women of African descent tend to be diagnosed younger, with more advanced, more aggressive disease, and are more likely to die of breast cancer [12–16].

To reduce disparities in the use of genetic services for breast cancer, the recent research has called for the creation of group-specific culturally relevant services based on perceived barriers identified by women of African descent [3,17–19]. In fact, research examining psychosocial predictors of uptake and use of*BRCA* genetic services suggests that women of African descent who decline genetic counseling report higher perceived barriers to genetic services [20], including negative affect, anticipation of adverse emotional reactions related to test results, concerns about stigmatization and confidentiality, as well as family-related worry and guilt [20–23]. However, little is known about potential within-group differences that may underlie such perceived barriers to *BRCA* genetic services.

To date, acculturation remains a relatively unexplored potential within-group difference that may underlie perceived barriers to *BRCA1/2* genetic services in women of African descent. Acculturation is traditionally defined as the degree to which the majority culture is adopted by a minority culture [24], with more recent accounts incorporating the process of ethnic groups exchanging cultural elements and complexes [25]. There are a range of approaches that currently exist for the assessment of acculturation, including measuring nativity, language use, proportion or years residence in the US, and cultural immersion [26–29], although there is no clear consensus on most useful measures. Although a burgeoning body of research addresses the role of acculturation in cancer outcomes for Latinos [30–33], there is a surprising lack of research reflecting the acculturation-related context and heterogeneity of the African-descent population in the US, 6% of which is foreign born and 10% of which has foreign ancestry [34,35]. In a diverse metropolitan setting such as New York City, documenting this heterogeneity is even more critical as approximately 25% of the African-descent population is Caribbean immigrants [36]. Examining individuals of African descent by subgroups may better reflect variations in health [37–39]; rates of breast cancer incidence and screening behaviors may vary by acculturation within individuals of African descent [40,41].

Furthermore, acculturation represents a complex psychological process of adaptation to stress, including changes in lifestyle, behaviors, beliefs, values, and identity as a result of contact with different cultural groups [42,43]. Although Caribbean women of African descent may initially have lower rates of psychological illnesses compared with US-born individuals of African descent [35], with increasing generation status, immigrants may become faced with the 'double burden of acculturation', as they acclimate to both mainstream America and Black America. Through processes of externally ascribed racial categorization, Caribbean immigrants may undergo exposure to increased levels of minority status and inequalities, making this subpopulation particularly vulnerable to increased risks of psychological stress and illnesses [35,44–46]. Combined with the recent literature documenting the need for within-group comparisons of psychological functioning in women of African descent at increased risk of breast and ovarian cancer, specifically breast cancer-specific distress [47], exploration of psychological predictors thus inevitably becomes linked to any study examining the potential association of acculturation and perceived barriers of *BRCA1/2* testing.

The goal of this study was to fill a gap in the current research by examining the relationship of acculturation and breast cancer-specific distress with perceived barriers to genetic testing among a diverse sample of women of African descent in New York City at increased risk of hereditary breast and/or ovarian cancer. Study outcomes were chosen as they have been previously validated and measured for use within urban African-American women to examine perceived barriers of genetic testing for breast cancer susceptibility [20]. These previously validated measures for perceived barriers include: (1) anticipation of negative emotional reactions, (2) stigma, (3) confidentiality concerns, (4) family-related worry, and (5) family-related guilt associated with genetic testing for breast cancer [20]. The primary aim was to investigate the potential association between acculturation and perceived barriers to genetic testing within women of African descent. A secondary aim was to explore the potential associations of breast cancer-specific distress with perceived barriers of genetic testing, as breast cancer-specific distress has previously been identified as a predictor of *BRCA* counseling and testing decisions within African-American women [20].

Methods

Study setting and population

We analyzed baseline information on 146 women of African descent available from a larger longitudinal study examining *BRCA1/2* decision-making and the psychosocial impact of standard genetic counseling versus culturally tailored genetic counseling in women at increased risk. The participants were recruited in the greater New York City area via an existing study on biobehavioral factors and breast cancer risk as well as through community outreach. A trained research assistant explained the study to potential participants and completed a family history form to determine eligibility based on family history suggestive of breast and/or ovarian cancer. Although there are different models and risk assessments related to the probability of carrying a *BRCA1/2* mutation, for this study women were considered eligible if they met the criteria of at least one of the three commonly used *BRCA1/2* risk estimation models (*BRCA*Pro, Penn, Myriad) [48–50]. Additional eligibility criteria included: women who self-identified as being of African descent, age 18 or older, English speaking, able to provide consent, and had not previously undergone genetic counseling or testing for hereditary breast or ovarian cancer. Women who were pregnant (based on participant disclosure) were excluded from this study, as pregnancy may cause additional distress that could impact concerns about genetic testing for breast and/or ovarian cancer. After the determination of eligibility by the research assistant, consent forms were mailed to all eligible women who met the study criteria. Following the collection of baseline information through a telephone interview, all participants were given the option of receiving free genetic services for *BRCA1/2*. The participants were then randomly assigned to one of the two types of genetic counseling (standard genetic counseling versus culturally tailored genetic counseling) and followed up at 1 month to determine their decision-making related to *BRCA1/2* genetic testing. For the cross-sectional analysis presented in this study, we focus only on the baseline data collected from telephone interviews, conducted by trained research assistants and including questions related to sociodemographics, psychological factors, cancer history, and attitudes and beliefs about *BRCA* genetic testing. Study protocols were approved by Mount Sinai's Institutional Review Board.

Measures

Predictors

Acculturation-related predictors: Acculturation-related predictors included participants' nativity (foreign versus US born) and proportion of one's life spent living in the US.

Although there are numerous ways to measure acculturation, these measures were selected as they have been previously identified in immigrants (Latinos) as influential factors affecting cancer screening uptake and knowledge and beliefs and attitudes about genetic testing and were therefore hypothesized to influence perceived barriers to genetic testing among women of African descent in this study [30,51–54]. In addition, selection of acculturation measures was limited by the baseline interview, which did not collect information on cultural immersion.

Breast cancer-specific distress: The Impact of Events Scale (IES) [55], including total score and intrusive and avoidance symptoms subscales, was used to assess breast cancer-specific distress. This scale was chosen as it has previously been identified as a psychosocial predictor of *BRCA* counseling and testing decisions among urban African-American women and therefore may be applicable to women of African descent [20]. All items were measured on a 4-point Likert scale (weighted as 'not at all' = 0, 'rarely' = 1, 'sometimes' = 3, and 'often' = 5). The intrusive symptoms subscale included seven items measuring intrusive ideation associated with the stressor of breast cancer (range = 0–35). The avoidance symptoms subscale included eight items measuring avoidance stress associated with the stressor of breast cancer (range = 0–40). The IES total included all 15 items (range = 0–75). The internal reliability of these measures was considered good ($\alpha = 0.91$ for IES total, $\alpha = 0.83$ for intrusion, and $\alpha = 0.86$ for avoidance).

Covariates

Sociodemographic background factors—Sociodemographic background factors included participants' age, race/ethnicity, education, income, marital status, and insurance status.

Breast and/or ovarian cancer history—Information about participants' personal diagnosis and family history of breast and/or ovarian cancer was included.

Outcomes

The baseline interview provided a one-paragraph description in layman's terms of the hereditary basis of breast and ovarian cancer and how genetic tests may be used to determine which family members have inherited a genetic mutation. The participants were asked how much they agreed or disagreed with a series of statements about the potential benefits and barriers of genetic testing, knowing that a blood test for inherited breast cancer is currently available. This study assessed five perceived barriers to genetic testing as described in Table 1. These outcomes have previously been validated for use in African-American women and examined as potential cons of *BRCA* testing [20] and were created based on previous research

[56–58]. All questions were measured on a 5-point Likert-type scale (strongly disagree to strongly agree), with total scores computed by summing individual questions and taking the average (range = 1–5). Internal reliability of all scales was considered adequate ($\alpha = 0.68$ for anticipation of negative emotional reactions, $\alpha = 0.73$ for stigma, $\alpha = 0.72$ for confidentiality concerns, $\alpha = 0.62$ for family-related worry, and $\alpha = 0.65$ for family-related guilt associated with genetic testing).

Analytic plan—After computing basic descriptive statistics, we compared foreign-born and US-born women of African descent in terms of sociodemographics, cancer history, and psychological factors using χ^2-tests and *t*-tests. Crude univariate linear regression analyses tested each predictor (acculturation factors and breast cancer-specific distress) and covariate individually and its potential association with study outcomes. Multivariable linear regression models were developed separately for each study outcome with the following steps: All significant variables ($p \leq 0.10$) in univariate analyses were chosen as covariates for inclusion in the candidate short list for multivariable models. A forward selection test was conducted as the automatic statistical procedure of choice to control for potential problems of collinearity. Owing to a relatively small sample size, a level of significance of $p \leq 0.10$ was chosen as most appropriate for determining initial entry into the forward selection test. Variables significant from the forward selection test were included in the final multivariable linear regression models. All other covariates independently associated with the outcomes or with significant differences found between foreignborn and US-born women were added one by one to test for potential confounding. Any such covariates producing a change of at least 20% in the β's of predictors already in the model (from forward selection) were considered to be confounders and included in the final models. Any theoretically necessary sociodemographic variables were also added. A level of $p \leq 0.05$ was used to determine the overall statistical significance of variables in the final model. The percentage of the variability explained by the final multivariable linear regression model was computed using an R^2-test. SAS software package v.9.1.3 was used to conduct all statistical procedures.

Results

Sample characteristics

Sample characteristics are presented in Table 2. One hundred and forty-six women were included in the sample. The participants were divided between US born (56%) and foreign born (44%), of which the majority emigrated from Caribbean countries (89%). The mean proportion of years lived in the US among immigrants was 0.4 (SD = 0.3) and the mean age of the participants was 45.8 (SD = 9.6; min = 22, max = 79). The majority of participants had incomes ≥$20 000/year, had attained more than a high school diploma, were not currently married, and were insured. Most women had a personal diagnosis (70%) and/or family history of breast and/or ovarian cancer (81%). The mean total score for the IES scale was 25.2. (SD = 17.3; min = 0, max = 60), suggesting moderate distress related to breast cancer [59]. Sociodemographic comparisons found that US-born women of African descent were more likely to have attained a high school education, make≥$20 000/year, and be insured compared with foreign-born women of African descent.

Univariate results

Table 3 reports the significant unadjusted predictors of the study outcomes.

Anticipation of negative emotional reactions related to genetic testing—Results indicate that foreign-born women of African descent reported more anticipation of negative emotional reactions related to genetic testing for breast cancer compared with US-born women of African descent, although proportion of years in the US was not related to this outcome.

Other significant predictors included education and breast cancer-specific distress (total IES score, intrusive, and avoidance symptoms).

Stigma related to genetic testing—Age was an independent predictor of stigma related to genetic testing.

Confidentiality concerns related to genetic testing—Independent predictors of confidentiality concerns related to genetic testing were education, income, breast cancer-specific distress (avoidance symptoms), and family history of breast and/or ovarian cancer.

Family-related worry associated with genetic testing—For family-related worry associated with genetic testing, independent predictors included education and breast cancer-specific distress (IES total and intrusive symptoms).

Family-related guilt associated with genetic testing—Variables significant in univariate analysis for family-related guilt included breast cancer-specific distress (IES total, intrusive, and avoidance symptoms) and family history of breast and/or ovarian cancer.

Multivariate results

Table 4 reports the final multivariate results for models that included significant acculturation factors and breast cancer-specific distress as predictors of perceived barriers to genetic testing. In these final models, age, family, and personal history of breast cancer were considered theoretically necessary (if not otherwise previously entered into the model) as they have been shown to influence breast cancer risk and screening practices and beliefs, attitudes, and concerns about genetic testing in women of African descent [60,61].

Anticipation of negative emotional reactions related to genetic testing—In testing the primary study aim, we found that foreign-born women of African descent reported more anticipation of negative emotional reactions related to genetic testing for cancer risk compared with US-born women of African descent ($\beta = 0.26$; SE = 0.11; $p = 0.01$), controlling for relevant factors. Related to the secondary study aim, we also found that women who had higher avoidance symptoms for breast cancer-specific distress reported more anticipation of negative emotional reactions related to genetic testing for cancer risk ($\beta = 0.02$; SE = 0.005; $p<0.0001$).

Confidentiality concerns related to genetic testing—In the final multivariate model adjusted for relevant factors, women who had higher avoidance symptoms for breast cancer-specific distress reported more confidentiality concerns related to genetic testing ($\beta = 0.02$; SE = 0.01; $p = 0.02$).

Family-related guilt associated with genetic testing—Breast cancer-specific distress (avoidance symptoms) was positively related to family-related guilt associated with genetic testing ($\beta = 0.02$; SE = 0.01; $p = 0.0009$) in the final multivariate model, adjusted for relevant factors.

Discussion

These results demonstrated that acculturation (specifically nativity) and breast cancer-specific distress may represent independent factors associated with perceived barriers to genetic testing among women of African descent. First, we found that foreign-born women of African descent reported more anticipation of negative emotional reactions about genetic testing compared with US-born women of African descent. Second, breast cancer-specific distress was also independently related to this perceived barrier to genetic testing. In this study, breast cancer-specific distress did not vary based on acculturation and therefore did not mediate the relationship between nativity and anticipation of negative emotional reactions. These results may contradict previous research identifying different levels of psychological stress in Caribbean immigrants compared with US-born women of African descent [35,45], at least for breast cancer-specific distress. However, we may speculate that other factors that were not measured here may be potential mediators of a relationship between nativity and anticipation of negative emotional reactions related to genetic testing, including acculturative stress and social support. Acculturative stress occurs when individuals face psychological problems as a result of the acculturation process [62]. Among Latinos, acculturative stress has been associated with negative emotional states and poorer psychological functioning [63,64] and may similarly apply to Caribbean immigrants of African descent, thereby impacting emotional reactions to genetic testing. In this study, US-born individuals of African descent may perceive a greater sense of support from family and friends compared with foreign-born individuals of African descent, decreasing the likelihood of anticipation of negative emotional reactions to genetic testing in US born. Meanwhile, among immigrants, social support may mediate a relationship between acculturative stress and perceived emotional reactions to genetic testing, as research with Latinos found that individuals reporting high acculturative stress with high levels of perceived social support reported fewer anxiety and depressive symptoms [63].

These results also revealed a positive relationship between breast cancer-specific distress and barriers to genetic testing, including anticipation of negative emotional reactions, confidentiality concerns, and family-related guilt. Although research has examined the impact of genetic testing on psychological distress [65,66], to date little is known about how psychological distress may influence genetic testing beliefs. Results found remarkably high levels of breast cancer-specific distress across women in our sample, even higher than elevated levels of distress during genetic counseling and testing reported in the recent research among African-American women at increased risk of hereditary breast and ovarian cancer [47]. Further, the positive association of breast cancer-specific distress (avoidance) and anticipation of negative emotional reactions related to genetic testing suggests a concordance between the current trauma/subjective stress and anticipation of stress. Finally, women who more often avoid thinking about breast cancer also reported more confidentiality concerns and family-related guilt related to genetic testing, suggesting these women may be particularly worried about matters of personal privacy, disclosure, and stress caused to their family.

It is unclear how these factors may ultimately impact the use of genetic services for breast cancer. Previous research has associated participation in genetic testing with increased anxiety and worry due to ambiguity and uncertainty presented by questions of whether and when cancer will develop [58,67]. Although behavior change theory postulates that negative emotional reactions may drive the use of genetic services for breast cancer [68–70], the current research documents both a negative and a positive effect of emotional reactions on genetic service use [3,7,20]. High levels of fear may lead to increased vigilance and use of genetic services [3,7, 71] or act as a deterrence to such use [3,20].

Clinically, these results support the use of genetic counseling to help alleviate emotional fears arising from concerns about receiving a positive test result among foreign-born women of African descent and among those with high levels of breast cancerspecific distress. Endorsed by the American Society of Clinical Oncologists, pre- and post-test genetic counseling is often a prerequisite for genetic testing and is useful for providing education about genetic testing as well as explaining psychological and social consequences of testing to the patient [72,73]. Genetic counseling, which provides psychological reinforcement, informs women of how they can make use of genetic testing results, and addresses the emotional repercussions stemming from genetic testing, may be particularly suitable to the needs of women of African descent [3,58,60]. Previous research shows that counseling, which includes personalized exploration of psychosocial issues in genetic testing, increases intentions to be tested and provision of a blood sample in women of African descent compared with information-only approaches [19]. For women of African descent with high levels of breast cancer-specific distress, as found in this study, genetic counseling may play less of an information-seeking role but instead represent more of an emotion management strategy [20].

Ultimately, these results contribute to the previous literature by highlighting the increasing need for culturally based interventions that accurately address the perceptions of women of African descent toward genetic services [3,17–19,74]. Furthermore, studies that provide a greater understanding of how cultural background may influence reactions to genetic services will ultimately influence the design of more culturally sensitive protocols [19]. Based on our results, we argue that acculturation is an important cultural influence that may impact perceived barriers related to *BRCA* genetic testing. For this reason, it is important that genetic counselors should consider such possible acculturation-related differences within women of African-descent populations in order to ensure that decisions are fully informed and culturally appropriate. Ultimately, by better understanding how nativity shapes the perceptions of genetic services within women of African descent, we will be better equipped to develop interventions that successfully address these perceptions [3,61].

For example, previous research with multicultural populations suggests that barriers to communication about genetic testing may occur when there is incompatibility between ‘Western’ and traditional beliefs [75]. In fact, culturally tailored genetic counseling for women of African descent, which attempts to overcome such communication barriers, has found that women receiving this format were more likely to report lessened worries about genetic testing compared with women undergoing standard genetic counseling [17]. In the light of study results demonstrating higher levels of anticipation of emotional reactivity related to genetic testing in foreign-born women of African descent, it is argued that culturally tailored counseling works with immigrant participants specifically to identify ways to reduce this reactivity. Furthermore, our secondary finding that breast cancer-specific distress was significantly related to perceived barriers to genetic testing underscores the need for genetic counseling to also consider the role of affective factors among women of African descent.

This study has several limitations. Owing to our small sample size and concerns about low power, we neither conduct analyses differentiating between the Caribbean and non-Caribbean foreign-born population nor examine possible country of origin differences. While this study sought to reveal the heterogeneity of African-descent individuals, some potential subgroup differences may have unfortunately been masked. For example, research suggests that the subcategory of African-descent Caribbean immigrants may mask variations in mental health [35]. Further, as noted earlier, there are many ways to measure acculturation and the selection of acculturation measures used in this study (nativity and proportion years in the US) was limited by variables available from the baseline interview. In addition, acculturative stress and social support were not measured and may serve to mediate a relationship between nativity and perceived negative emotional reactions about genetic testing [62–64], along with other more general measures of psychological well-being, including depression and anxiety. Future studies incorporating these acculturation and psychological-related factors are thus warranted.

While the perceived barriers chosen as outcomes for this study were previously validated and measured within African-American women [20], another limitation is that there may be other barriers to genetic testing that this study may not have addressed; future studies should thus include qualitative open-ended questions regarding barriers to genetic testing. In addition, as the majority of research conducted to date in this area has been atheoretical, future studies could benefit from the incorporation of theoretically driven models, such as the Health Belief

Model [76–78], to analyze other factors including perceived severity and risk, barriers, and benefits that may be related to the uptake of genetic testing.

Generalizability of study results may also be limited, as this study was conducted within a diverse sample of individuals of African descent in New York City; results may only be applicable to metropolitan areas in the US with similarly diverse samples. Possible selection bias for participation in the larger study may also limit the generalizability of the study results as these women are likely to be more open to the use of genetic testing services than would be the case in the general population. Furthermore, since the majority of participants were insured, women may have faced substantially different barriers to genetic services compared with an uninsured population. Qualitative research with women of African descent describes how the cost of genetic services is one of the most influential factors inhibiting the decision to receive these services [3]. A final limitation inherent to the cross-sectional nature of this analysis is that we cannot rule out the direction of causality for breast cancer-specific distress and its relationship with perceived barriers to genetic testing.

Conclusion

In conclusion, results uniquely contribute to the literature by suggesting an influence of nativity and breast cancer-specific distress on perceived barriers to genetic testing within women of African descent. The potential utility of culturally tailored genetic counseling services taking into account such influences and addressing emotional and psychological concerns of women considering genetic testing for breast cancer should be investigated.

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References

1. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007;25(11): 1329–1333. [PubMed: 17416853]
2. The Breast Cancer Linkage Consortium. Cancer risks in*BRCA2* mutation carriers. The Breast Cancer Linkage Consortium. J Natl Cancer Inst 1999;91:1310–1316. [PubMed: 10433620]
3. Ford ME, Alford SH, Britton D, McClary B, Gordon HS. Factors influencing perceptions of breast cancer genetic counseling among women in an urban health care system. J Genet Couns 2007;16:735–753. [PubMed: 17701328]
4. Grann VR, Jacobson JS, Thomason D, Hershman D, Heitjan DF, Neugut AI. Effect of prevention strategies on survival and quality-adjusted survival of women with *BRCA1*/2 mutations: an updated decision analysis. J Clin Oncol 2002;20(10):2520–2529. [PubMed: 12011131]
5. Hall MJ, Olopade OI. Disparities in genetic testing: thinking outside the *BRCA* box. J Clin Oncol 2006;24(14):2197–2203. [PubMed: 16682739]
6. Olopade OI. Genetics in clinical cancer care: a promise unfulfilled among minority populations. Cancer Epidemiol Biomarkers Prev 2004;13(11):1683–1686. [PubMed: 15533893]
7. Armstrong K, Micco E, Carney A, Stopfer J, Putt M. Racial differences in the use of*BRCA1/2* testing among women with a family history of breast or ovarian cancer. J Am Med Assoc 2005;293:1729–1736.
8. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: a comparative analysis of *BRCA1* and *BRCA2* mutations in American families of European and African ancestry. J Am Med Assoc 2005;294:1925–1933.

9. Frank TS, Deffenbaugh AM, Reid JE, et al. Clinical characteristics of individuals with germline mutations in *BRCA1* and *BRCA2*: analysis of 10,000 individuals. J Clin Oncol 2002;20:1480–1490. [PubMed: 11896095]
10. Gao Q, Tomlinson G, Das S, et al. Prevalence of BRCA1 and*BRCA2* mutations among clinic-based African American families with breast cancer. Hum Genet 2000;107:186–191. [PubMed: 11030417]
11. Panguluri RCK, Brody LC, Modali R, et al. BRCA1 mutations in African Americans. Hum Genet 1999;105:28–31. [PubMed: 10480351]
12. Cancer Facts and Figures 2003. Atlanta, GA: American Cancer Society Inc.; 2007. American Cancer Society.
13. Bickell NA, Wang JJ, Oluwole S, et al. Missed opportunities: racial disparities in adjuvant breast cancer treatment. J Clin Oncol 2006;24(9):1357–1362. [PubMed: 16549830]
14. Li CI. Racial and ethnic disparities in breast cancer stage, treatment and survival in the United States. Ethn Dis 2005;15(2 Suppl 2):S5–S9. [PubMed: 15822829]
15. Li CI, Malone KE, Daling JR. Differences in breast cancer stage, treatment and survival by race and ethnicity. Arch Intern Med 2003;163:49–56. [PubMed: 12523916]
16. Bayer-Chammard A, Taylor TH, Anton-Culver H. Survival differences in breast cancer among racial/ethnic groups: a population-based study. Cancer Detect Prev 1999;23:463–473. [PubMed: 10571656]
17. Charles S, Kessler L, Stopfer JE, Domcheck S, Halbert CH. Satisfaction with genetic counseling for *BRCA1* and *BRCA2* mutations among African American women. Patient Educ Couns 2006;63:196–204. [PubMed: 16533589]
18. Baty BJ, Kinney AY, Ellis SM. Developing culturally sensitive cancer genetics communication aids for African Americans. Am J Med Genet 2003;118:146–155. [PubMed: 12655495]
19. Lerman C, Hughes C, Benkendorf JL, Biesecker B. Racial differences in testing motivation and psychological distress following pretest education for *BRCA1* gene testing. Cancer Epidemiol Biomarkers Prev 1999;8:361–367. [PubMed: 10207641]
20. Thompson HS, Valdimarsdottir HB, Duteau-Buck C, et al. Psychosocial predictors of *BRCA* counseling and testing decisions among urban African-American women. Cancer Epidemiol Biomarkers Prev 2002;11:1579–1585. [PubMed: 12496047]
21. Donovan KA, Tucker DC. Knowledge about genetic risk for breast cancer and perceptions of genetic testing in a sociodemographically diverse sample. J Behav Med 2000;23:15–36. [PubMed: 10749009]
22. Matthews AK, Cummings S, Thompson S, Wohl V, List M, Olopade OI. Genetic testing of African Americans for susceptibility to inherited cancers: use of focus groups to determine factors contributing to participation. J Psychosoc Oncol 2000;18(2):1–19.
23. Hughes C, Fasaye GA, LaSalle VH, Finch C. Sociocultural influences on participation in genetic risk assessment and testing among African American women. Patient Educ Couns 2003;51:107–114. [PubMed: 14572939]
24. Suarez L. Pap smear and mammogram screening in Mexican-American women: the effects of acculturation. Am J Public Health 1994;84(5):742–746. [PubMed: 8179042]
25. Abraido-Lanza AF, Armbrister AN, Florez KR, Aguirre AN. Toward a theory-driven model of acculturation in public health research. Am J Public Health 2006;96:1342–1346. [PubMed: 16809597]
26. Caetano R. Alcohol use and depression among U.S. Hispanics. Br J Addict 1987;82:1245–1251. [PubMed: 3480741]
27. Marin G, Sabogal F, Marin BV, Otero-Sabogal R, Perez-Stable EJ. Development of a short acculturation scale for Hispanics. Hisp J Behav Sci 1987;9:183–205.
28. Marin G, Gamba R. A new measurement of acculturation for Hispanics: the bidimensional acculturation scale for Hispanics (BAS). Hisp J Behav Sci 1996;18(3):297–316.
29. Snowden LR, Hines AM. A scale to assess African American acculturation. J Black Psychol 1999;25:36–47.
30. Echeverria SE, Carrasquillo O. The roles of citizenship status, acculturation, and health insurance in breast and cervical cancer screening among immigrant women. Med Care 2006;44:788–792. [PubMed: 16862042]

31. Abraido-Lanza AF, Chao MT, Gates CY. Acculturation and cancer screening among Latinas: results from the National Health Interview Survey. Ann Behav Med 2005;29(1):22–28. [PubMed: 15677297]
32. Eschbach K, Mahnken JD, Goodwin JS. Neighborhood composition and incidence of cancer among Hispanics in the United States. Cancer 2005;103:1036–1044. [PubMed: 15672387]
33. John EM, Phipps AI, Davis A, Koo J. Migration history, acculturation, and breast cancer risk in Hispanic women. Cancer Epidemiol Biomarkers Prev 2005;14:2905–2913. [PubMed: 16365008]
34. Schmidley, AD.; Gibson, C. US Census Bureau, Current Population Reports, Series P23–195. Washington, DC: US Government Printing Office; 1999. Profile of the foreign-born population in the United States.
35. Williams DR, Haile R, Gonzalez HM, Neighbors H, Baser R, Jackson JS. The mental health of black Caribbean immigrants: results from the National Survey of American Life. Am J Public Health 2007;97(1):52–59. [PubMed: 17138909]
36. Logan, JR.; Deane, G. Black Diversity of Metropolitan America. Albany, NY: University at Albany Lewis Mumford Center for Comparative Urban and Regional Research; 2003.
37. Kington, RS.; Nickens, HW. Racial and ethnic differences in health: recent trends, current patterns, future directions. In: Smelser, NJ.; Wilson, WJ.; Mitchell, F., editors. America Becoming: Racial Trends and Their Consequences. Vol. vol. II. Washington, DC: National Research Council; 2001. p. 253-310.
38. Williams DR, Jackson JS. Race/ethnicity and the 2000 census: recommendations for African American and other Black populations in the United States. Am J Public Health 2000;90:1728–1730. [PubMed: 11076240]
39. Magai C, Consedine N, Conway F, Neugut A, Culver C. Diversity matters: unique populations of women and breast cancer screening. Cancer 2004;100:2300–2307. [PubMed: 15160332]
40. Fruchter RG, Nayeri K, Remy JC, et al. Cervix and breast cancer incidence in immigrant Caribbean women. Am J Public Health 1990;80:722–724. [PubMed: 2343960]
41. Brown WM, Consedine NS, Magai C. Time spent in the United States and breast cancer screening behaviors among ethnically diverse immigrant women: evidence for acculturation? J Immigr Minor Health 2006;8:347–358. [PubMed: 16645898]
42. Al-Omari H, Pallikkathayil L. Psychological acculturation: a concept analysis with implications for nursing practice. J Transcult Nurs 2008;19(2):126–133. [PubMed: 18263848]
43. Caplan S. Latinos, acculturation, and acculturative stress: a dimensional concept analysis. Policy Polit Nurs Pract 2007;8(2):93–106. [PubMed: 17652627]
44. Kasinitz, P. Caribbean New York: Black Immigrants and the Politics of Race. Ithaca, NY: Cornell University Press; 1992.
45. Williams, DR. Race, stress and mental health: findings from the Commonwealth Minority Health Survey. In: Hogue, C.; Hargraves, M.; Scott-Collins, K., editors. Minority Health in America: Findings and Policy Implication from the Commonwealth Fund Minority Health Survey. Baltimore, MD: Johns Hopkins University Press; 2000. p. 209-243.
46. Vickerman, M. Crosscurrents: West Indian Immigrants and Race. New York, NY: Oxford University Press; 1999.
47. Halbert CH, Kessler L, Collier A, Wileyto PE, Brewster K, Weathers B. Psychological functioning in African American women at an increased risk of hereditary breast and ovarian cancer. Clin Genet 2005;68:222–227. [PubMed: 16098010]
48. Parmigiani G, Berry DA, Aquilar O. Determining carrier probabilities for breast cancer susceptibility genes *BRCA1* and *BRCA2*. Am J Hum Genet 1998;62:145–158. [PubMed: 9443863]
49. Frank TS, Manley SA, Olopade OI, et al. Sequence analysis of *BRCA1* and *BRCA2*: correlation of mutations with family history and ovarian cancer risk. J Clin Oncol 1998;16(7):2417–2425. [PubMed: 9667259]
50. Couch FJ, DeShano ML, Blackwood MA, et al. *BRCA1* mutations in women attending clinics that evaluate the risk of breast cancer. N Engl J Med 1997;336:1409–1415. [PubMed: 9145677]
51. Sussner KM, Thompson HS, Valdimarsdottir HB, Redd WH, Jandorf L. Acculturation and familiarity with, attitudes towards and beliefs about genetic testing for cancer risk within Latinas in East Harlem, New York City. J Genet Couns. 2008DOI: 10.1007/s10897-008-9182-z.

52. Vadaparampil ST, Wideroff L, Breen N, Trapido E. The impact of acculturation on awareness of genetic testing for increased cancer risk among Hispanics in the year 2000 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev 2006;15(4):618–623. [PubMed: 16614100]
53. Rodriguez MA, Ward LM, Perez-Stable EJ. Breast and cervical cancer screening: impact of health insurance status, ethnicity and nativity of Latinas. Ann Fam Med 2005;3:235–241. [PubMed: 15928227]
54. Goel MS, Wee CC, McCarthy EP, Davis RB, NgoMetzger Q, Phillips RS. Racial and ethnic disparities in cancer screening: the importance of foreign birth as a barrier to care. J Gen Intern Med 2003;18 (12):1028–1035. [PubMed: 14687262]
55. Horowitz M, Wilner N, Alvarez W. Impact of Event scale: a measure of subjective stress. Psychosom Med 1979;41:209–218. [PubMed: 472086]
56. Jacobsen PB, Valdimarsdottir HB, Brown KL, Offit K. Decision making about genetic testing among women at familial risk for breast cancer. Psychosom Med 1997;59:459–466. [PubMed: 9316177]
57. Hughes C, Gomez-Caminero A, Benkendorf J, et al. Ethnic differences in knowledge and attitudes about *BRCA1* testing in women at increased risk. Patient Educ Couns 1997;32:51–62. [PubMed: 9355572]
58. Lerman C, Croyle RT. Emotional and behavioral responses to genetic testing for susceptibility to cancer. Oncology 1996;10:191–199. [PubMed: 8838261]
59. Coffey SF, Berglind G. Screening for PTSD in motor vehicle accident survivors using PSS-SR and IES. J Trauma Stress 2006;19(1):119–128. [PubMed: 16568464]
60. Lipkus IM, Iden D, Terrenoire J, Feaganes JR. Relationships among breast cancer concern, risk perceptions, and interest in genetic testing for breast cancer susceptibility among African-American women with and without a family history of breast cancer. Cancer Epidemiol Biomarkers Prev 1999;8:533–539. [PubMed: 10385144]
61. Halbert C, Kessler L, Stopfer JE, Domchek S, Wileyto EP. Low rates of acceptance of *BRCA1* and *BRCA2* test results among African American women at increased risk for hereditary breast–ovarian cancer. Genet Med 2006;8(9):576–582. [PubMed: 16980814]
62. Williams CL, Berry JW. Primary prevention of acculturative stress among refugees: application of psychological theory and practice. Am Psychol 1991;46:632–641. [PubMed: 1952422]
63. Crockett LJ, Iturbide MI, Torres Stone RA, McGinley M, Raffaelli M, Carlo G. Acculturative stress, social support, and coping: relations to psychological adjustment among Mexican American college students. Cultur Divers Ethnic Minor Psychol 2007;13(4):347–355. [PubMed: 17967103]
64. Hovey JD, King CA. Acculturative stress, depression, and suicidal ideation among immigrant and second-generation Latino adolescents. J Am Acad Child Adolesc Psychiatry 1996;35:1183–1192. [PubMed: 8824062]
65. Reichelt JG, Moller P, Heimdal K, Dahl AA. Psychological and cancer-specific distress at 18 months post-testing in women with demonstrated *BRCA1* mutations for hereditary breast/ovarian cancer. Fam Cancer 2008;7:245–254. [PubMed: 18219587]
66. Schwartz MD, Peshkin BN, Hughes C, Main D, Isaacs C, Lerman C. Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. J Clin Oncol 2002;20(2):514–520. [PubMed: 11786581]
67. Croyle, R.; Lerman, C. Psychological impact of genetic testing. In: Croyle, R., editor. Psychological Effects of Screening for Disease Prevention and Detection. Oxford, UK: Oxford University Press; 1994.
68. Janis, I. Effects of fear arousal on attitudinal change: recent development on theory and experimental research. In: Berkowitz, L., editor. Advances in Experimental Social Psychology. New York: Academic Press; 1967. p. 166-244.
69. Leventhal, H. Findings and theory in the study of fear communications. In: Berkowitz, L., editor. Advances in Experimental Social Psychology. Vol. vol. 3. San Diego, CA: Academic Press; 1970. p. 119-186.
70. Lobell M, Bay RC, Rhoads KV, Keske B. Barriers to cancer screening in Mexican-American women. Mayo Clin Proc 1998;73(4):301–308. [PubMed: 9559032]

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71. Dorval M, Bouchard K, Maunsell E, et al. Health behaviors and psychological distress in women initiating *BRCA1/2* genetic testing: comparison with control population. J Genet Couns 2008;17:314–326. [PubMed: 18481164]
72. Schneider KA. Genetic counseling for *BRCA1/BRCA2* testing. Genet Test 1997;1:91–98. [PubMed: 10464632]
73. American Society of Clinical Oncology. Policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21(12):2397–2406. [PubMed: 12692171]
74. Pierce RL. African-American cancer patients and culturally competent practice. J Psychosoc Oncol 1997;15:1–17.
75. Barlow-Stewart K, Yeo SS, Meiser B, Goldstein D, Tucker K, Eisenbruch M. Toward cultural competence in cancer genetic counseling and genetics education: lessons learned from Chinese-Australians. Genet Med 2006;8(1):24–32. [PubMed: 16418596]
76. Rosenstock IM. Historical origins of the health belief model. Health Educ Monogr 1974;2:328–335.
77. Janz NK, Becker MH. The health belief model: a decade later. Health Educ Q 1984;11(1):1–47. [PubMed: 6392204]
78. Strecher, VJ.; Rosenstock, IM. The health belief model: explaining health behavior through expectancies. In: Glanz, K.; Lewis, FM.; Rimer, BK., editors. Health Behavior and Health Education: Theory, Research, and practice. San Francisco, CA: Jossey-Bass; 1997. p. 4-59.

Table 1

Description of perceived barriers related to genetic testing

Perceived barriers related to genetic testing	**Items included**	**Internal reliability (α)**
(1) Anticipation of negative emotion reactions	• I would be frightened if I were found to carry the gene mutation • Knowing that I carry the gene mutation would leave me in a state of hopelessness and despair • I would consider suicide if I were found to carry the gene mutation for breast cancer • If I underwent genetic testing for cancer, I would not be able to handle it emotionally	0.68
(2) Stigma	• If I were found to carry the gene mutation for breast cancer, I would feel singled out • If I were found to carry a gene mutation for cancer, it would cause others to view me negatively • I would be ashamed if I were found to carry the gene mutation	0.73
(3) Confidentiality concerns	• If I were found to carry the gene mutation, I would worry the results would not stay confidential • Being tested for the gene mutation could jeopardize my insurance coverage	0.72
(4) Family-related worry	• If I were found to carry the gene mutation for breast cancer, I would worry about passing the gene to my children • Knowing that I carry the gene mutation would cause me to worry more about other family members who could be carriers (e.g. mother, sisters, daughters)	0.62
(5) Family-related guilt	• If I were found to carry the gene mutation for breast cancer, I would feel guilty if my daughter(s) developed breast cancer • I would feel guilty if one of my relatives had the gene mutation and I did not	0.65

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Table 2

Baseline statistics—perceived barriers related to genetic testing (GT) for cancer risk and comparison of foreign-born versus US-born women of African descent

Predictor variables	**Sample Mean (SD)**	***N* (%)**	**Foreign born *N* (%) or mean (SD)**	**US born *N* (%) or mean (SD)**	**χ^2- or *t*-test**	***p* Value**
Acculturation-related factors						
Nativity						
Foreign born	n/a	64 (44)	64 (100)	0 (0)	n/a	n/a
Caribbean	n/a	57 (89)	57 (89)	0 (0)	n/a	n/a
Non-Caribbean	n/a	7 (11)	7 (11)	0 (0)	n/a	n/a
US born	n/a	82 (56)	0 (0)	82 (100)	n/a	n/a
Proportion years lived in US						
Immigrants only	0.4 (0.3)	64	0.4 (0.3)	n/a	n/a	n/a
Psychological factors						
Breast cancer-specific distress						
Impact of Events Scale (IES total) (range = 0–75)	25.2 (17.3)	146	24.5 (16.9)	25.8 (17.7)	0.45	0.66
Intrusive symptoms (range5 0–35)	12.4 (8.5)	146	11.5 (7.9)	13.1 (8.9)	1.21	0.23
Avoidance symptoms (range5 0–40)	12.8 (10.0)	146	13.0 (10.3)	12.6 (9.8)	−0.25	0.80
Covariates						
Sociodemographics						
Age	45.8 (9.6)	146	45.7 (9.4)	45.8 (9.8)	0.06	0.95
Race/ethnicity						
Black/African American	n/a	75 (51)	5 (8)	70 (84)	86.5	< 0.000 1*
Black-West Indian/Caribbean	n/a	63 (43)	54 (86)	9 (11)	78.9	< 0.000 1*
Black-other	n/a	6 (4)	3 (5)	3 (4)	0.09	0.76
Black-African	n/a	2 (2)	1 (1)	1 (1)	0.03	0.86
Education						
≤ High school diploma	n/a	48 (33)	28 (44)	20 (24)	6.10	0.01*
≥ High school diploma	n/a	98 (67)	36 (56)	62 (76)		
Income						
≤ $19 999/year	n/a	44 (31)	25 (43)	19 (23)	6.26	0.01*
≥ $20 000/year	n/a	96 (67)	33 (57)	63 (77)		
Marital status						

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Predictor variables	**Sample Mean (SD)**	***N* (%)**	**Foreign born *N* (%) or mean (SD)**	**US born *N* (%) or mean (SD)**	**χ^2- or *t*-test**	***p* Value**
Currently married/living with	n/a	48 (33)	25 (39)	23 (28)	1.98	0.16
Not currently married/living with	n/a	98 (67)	39 (61)	59 (72)		
Insurance status						
Insured (public and private)	n/a	129 (88)	47 (76)	78 (98)	15.55	<0.0001*
Non-insured	n/a	17 (12)	15 (24)	2 (2)		
Cancer history						
Personal breast/ovarian cancer diagnosis						
Yes	n/a	99 (70)	44 (71)	55 (69)	0.08	0.78
No	n/a	43 (30)	18 (29)	25 (31)		
Family history breast/ovarian cancer						
Yes	n/a	113 (81)	46 (78)	67 (84)	0.75	0.39
No	n/a	26 (19)	13 (22)	13 (16)		
Outcome variables—perceived barriers to GT						
Anticipation of negative emotional reactions related to GT	1.9 (0.6)	146	2.0 (0.6)	1.8 (0.6)	−1.97	0.05*
Stigma related to GT	1.8 (0.6)	146	1.8 (0.6)	1.8 (0.6)	−0.3	0.71
Confidentiality concerns related to GT	2.3 (0.9)	146	2.3 (0.9)	2.3 (0.9)	0.3	0.75
Family-related worry associated with GT	3.8 (0.8)	144	3.8 (0.8)	3.7 (0.9)	−0.90	0.37
Family-related guilt associated with GT	2.5 (0.9)	144	2.4 (0.8)	2.5 (0.8)	0.45	0.65

* Significance level $p \leq 0.05$.

Table 3

Significant unadjusted predictor estimates of perceived barriers to genetic testing (GT) for cancer risk outcomes

Outcomes—perceived barriers to GT for cancer risk	Significant unadjusted predictors*	β Coefficient/parameter estimate (SE)
(1) Anticipation of negative emotional reactions related to genetic testing	Nativity	
	Foreign born versus US born	0.19 (0.09)
	Education	
	≤ High school versus ≥ high school	0.18 (0.10)
	Breast cancer-specific distress	
	IES total	0.01 (0.003)
	Intrusive symptoms	0.02 (0.005)
	Avoidance symptoms	0.02 (0.004)
(2) Stigma	Age	0.01 (0.004)
(3) Confidentiality concerns	Education	
	≤ High school versus ≥ high school	−0.27 (0.15)
	Income	
	≤ $19 999/year versus ≥ $20 000/year	−0.30 (0.16)
	Breast cancer-specific distress	
	Avoidance symptoms	0.01 (0.007)
	Family history breast/ovarian cancer	
	Yes versus no	0.41 (0.19)
(4) Family-related worry	Education	
	≤ High school versus ≥ high school	0.33 (0.14)
	Breast cancer-specific distress	
	IES total	0.01 (0.004)
	Intrusive symptoms	0.02 (0.01)
(5) Family-related guilt	Breast cancer-specific distress	
	IES total	0.01 (0.004)
	Intrusive symptoms	0.02 (0.01)
	Avoidance symptoms	0.02 (0.01)
	Family history breast/ovarian cancer	
	Yes versus no	0.60 (0.19)

*Significance level $p \leq 0.10$.

Table 4

Final multivariable models—adjusted predictors of perceived barriers to genetic testing (GT) outcomes

Final models—perceived barriers to GT outcomes	**Anticipation of negative emotional reactions related to GT**[a]		**Confidentiality Concerns associated with GT**[b]		**Family-related guilt associated with GT**[c]	
Characteristic	**β Coefficient/parameter estimate (SE)**	***p* Value**	**β Coefficient/ parameter estimate (SE)**	***p* Value**	**β Coefficient/ parameter estimate (SE)**	***p* Value**
Nativity						
Foreign born versus US born	0.26 (0.11)	0.01*	n/a	n/a	n/a	n/a
Breast cancer-specific distress						
Avoidance symptoms	0.02 (0.005)	<0.0001*	0.02 (0.01)	0.02*	0.02 (0.01)	0.0009*
Insurance						
1Yes versus no	0.27 (0.17)	0.11	n/a	n/a	n/a	
Income						
≤ $19 999/year versus	−0.10 (0.11)	0.38	−0.37 (0.17)	0.03*	n/a	n/a
≥$20 000/year						
Age	0.01 (0.005)	0.25	0.005 (0.01)	0.54	0.0001 (0.008)	0.99
Family history breast/ovarian cancer						
Yes versus no	0.11 (0.13)	0.40	0.49 (0.21)	0.02*	0.75 (0.20)	0.0002*
Personal history breast/ovarian cancer						
Yes versus no	−0.12 (0.11)	0.28	0.29 (0.18)	0.10	0.26 (0.17)	0.13

[a] R^2 = 0.19. Final model includes variables significant from forward selection procedure (nativity and breast cancer-specific distress-avoidance symptoms) plus confounders (insurance, income) and any theoretically necessary covariates (age, family, and personal history of breast/ovarian cancer).

[b] R^2 = 0.12. Final model includes variables significant from forward selection procedure (breast cancer-specific distress-avoidance symptoms, income, and family history of breast/ovarian cancer) plus confounders (none) and any theoretically necessary covariates (age and personal history of breast/ovarian cancer).

[c] R^2 = 0.17. Final model includes variables significant from forward selection procedure (breast cancer-specific distress-avoidance symptoms and family history of breast/ ovarian cancer) plus confounders (none) and any theoretically necessary covariates (age and personal history of breast/ovarian cancer).

* Significance level p≤0.05.

An Admixture Scan in 1,484 African American Women with Breast Cancer

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Abstract

African American women with breast cancer present more commonly with aggressive tumors that do not express the estrogen receptor (ER) and progesterone receptor (PR) compared with European American women. Whether this disparity is the result of inherited factors has not been established. We did an admixture-based genome-wide scan to search for risk alleles for breast cancer that are highly differentiated in frequency between African American and European American women, and may contribute to specific breast cancer phenotypes, such as ER-negative (ER−) disease. African American women with invasive breast cancer (*n* = 1,484) were pooled from six population-based studies and typed at ~1,500 ancestry-informative markers. We investigated global genetic ancestry and did a whole genome admixture scan searching for breast cancer–predisposing loci in association with disease phenotypes. We found a significant difference in ancestry between ER+PR+ and ER−PR− women, with higher European ancestry among ER+PR+ individuals, after controlling for possible confounders (odds ratios for a 0 to 1 change in European ancestry proportion, 2.84; 95% confidence interval, 1.13-7.14; *P* = 0.026). Women with localized tumors had higher European ancestry than women with non–localized tumors (odds ratios, 2.65; 95% confidence interval, 1.11-6.35; *P* = 0.029). No genome-wide statistically significant associations were observed between European or African ancestry at any specific locus and breast cancer, or in analyses stratified by ER/PR status, stage, or grade. In summary, in African American women, genetic ancestry is associated with ER/PR status and disease stage. However, we found little evidence that genetic ancestry at any one region contributes significantly to breast cancer risk or hormone receptor status. (Cancer Epidemiol Biomarkers Prev 2009;18(11):3110–7)

Introduction

Breast cancer incidence and mortality varies widely among women of different population groups in the United States. African American women have lower age-adjusted incidence of breast cancer compared with European Americans (1). However, breast cancer incidence is higher in African Americans who are 35 years of age or younger (2). African American women are also diagnosed, on average, with later stage of disease, larger

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tumors, and are more likely to present with lymph node metastases at the time of diagnosis (2, 3). Thus, despite the lower lifetime incidence of breast cancer among African American women compared with European American women, their breast cancer mortality rates are higher (4-6), particularly among younger women (7).

The expression of steroid hormone receptors (estrogen and progesterone receptors) in breast cancer tumors also varies substantially by population. African American women are diagnosed more frequently with estrogen receptor–negative (ER−) and progesterone receptor–negative (PR−) breast cancer compared with European American women (5, 7-9). In the Women's Health Initiative, 32% of breast cancers among postmenopausal African American women were ER− with poor/anaplastic grade in comparison to only 10% among European American women, a difference which remained after adjustment for multiple potentially confounding factors, including differential access to health care (10). Given the greater incidence of hormone receptor–negative, high-grade disease among African Americans, we hypothesized that there may be one or more genetic variants with increased frequency in populations of African origin, which predispose women to this more aggressive form of breast cancer.

Admixture mapping is a powerful approach for identifying genetic variants for common phenotypes that have large allele frequency differences between ancestral populations (11-14). Admixed populations are defined as populations in which two or more ancestral groups have been mixing over several generations. Recently admixed populations show extended linkage disequilibrium between markers that have a large difference in allele frequency between ancestral populations and are, therefore, informative about ancestry (ancestry-informative markers or "AIM"; refs. 13, 15). The principle of admixture mapping is to identify regions of the genome with greater estimated ancestry from one of the ancestral populations than the chromosomal average in individuals from an admixed group. These regions may highlight candidate risk loci that are associated with complex phenotypes. We have previously used this approach to identify risk variants for prostate cancer at 8q24 that are common in African American men and contribute to their increased disease incidence (16).

Here, we did an admixture-based genome-wide scan in 1,484 African American women with invasive breast cancer pooled from six population-based studies. Samples were typed at ~1,500 AIMs to search for loci that might harbor predisposing variants for breast cancer, and more specifically, loci that may contribute to specific breast cancer phenotypes, such as ER− disease, a trait which is more common in African American women.

Materials and Methods

Samples. This analysis includes samples from six population-based breast cancer studies described in brief below.

The Multiethnic Cohort Study. This study is a prospective cohort that includes >215,000 individuals from Hawaii and California (primarily Los Angeles) that was assembled between 1993 and 1996 (17, 18). The cohort is comprised predominantly of African Americans, Native Hawaiians, Japanese, Latinos, and European Americans. Beginning in 1994, blood samples were collected from incident breast cancer cases identified by cohort linkage to Surveillance, Epidemiology and End Results (SEER) registries, as well as a random sample of Multiethnic Cohort participants to serve as controls for genetic analyses. The present study includes 423 invasive African American breast cancer cases from the Multiethnic Cohort, ages 45 to 82 y at diagnosis.

The Los Angeles Component of the Women's Contraceptive and Reproductive Experiences Study. A population-based case control study that included African American and Caucasian women with invasive breast cancer and control subjects, ages 35 to 64 y (19). Incident cases diagnosed between 1994 and 1998 were identified by the Los Angeles SEER registry. This study contributed 384 invasive African American breast cancer cases to the scan.

The Learning the Influence of Family and the Environment Study. This study included invasive African American breast cancer cases from Los Angeles county, ages 20 to 49 y (20). Incident cases diagnosed between 2000 and 2003 were identified from the Los Angeles SEER registry. In the current study, we used DNA samples obtained from 140 invasive cases.

The Women's Circle of Health Study. This study included African American women, 20 to 65 y of age, newly diagnosed with a first primary, histologically confirmed breast cancer. Cases were identified from major metropolitan hospitals in New York City serving a large minority population, and from the eight counties in New Jersey bordering the Hudson River. The present study includes 194 invasive breast cancer cases.

The San Francisco Bay Area Breast Cancer Study. A population-based case-control study of breast cancer in Hispanic, African American, and non-Hispanic white women (21, 22). Incident cases of invasive breast cancer ages 35 to 79 y were identified through the Greater Bay Area Cancer Registry. The present analysis includes 191 African American breast cancer cases diagnosed between 1997 and 1999.

Northern California Site of the Breast Cancer Family Registry. The Breast Cancer Family Registry is an international collaboration of six academic and research institutions, established in 1995 with support from the U.S. National Cancer Institute to serve as a resource for genetic studies of breast cancer (23). The California site enrolled newly diagnosed breast cancer cases ages <65 y that were identified through the Greater Bay Area Cancer Registry. The present study includes 314 unrelated African American breast cancer cases diagnosed between 1995 and 2003.

Genotyping. Invasive breast cancer cases in these six studies (1,646) were genotyped for two AIM panels using the Illumina GoldenGate assay (each panel consisting of 1,536 AIMs). The Women's Circle of Health Study, San Francisco Bay Area Breast Cancer Study, and the Breast Cancer Family Registry samples (set 1, n = 699) were genotyped at the University of California, San Francisco with a phase 2 panel, which was first published by Reich et al. (24). From this panel, 196 markers were dropped because of failure and replaced with 196 additional markers (phase 2 panel version b; Supplementary Table S1, 196 new SNPs are highlighted). A set of markers was selected based on allele frequency differences in West Africans from London and Europeans from Centre d'Etude du Polymorphisme Humain and they were scored by the Illumina snp_score, which predicts how well the markers will be genotyped. Fst and δ values (two measures of allele frequency difference between populations) were calculated for the markers. A total of 196 evenly spaced markers with the top scores for the Illumina snp_score and with the highest Fst (>0.4) and δ values (>0.6) were selected to include in the new phase 2 panel version b. The Multiethnic Cohort, Women's Contraceptive and Reproductive Experiences (CARE), and Learning the Influence of Family and the Environment (LIFE) studies (set 2, n = 947) were genotyped at the University of Southern California Genomics Core Laboratory with a phase 3 AIM panel.[15]

We genotyped the 1,646 samples for a total of 2,427 AIMs. For each set, we removed samples and SNPs that did not pass our quality control criteria. We removed samples with missing histology (set 1, n = 88; set 2, n = 0) and those with low call rates (defined as <85%) or that showed genotypes that are not consistent with the expectation based on the estimated global European ancestry (ref. 25; set 1, n = 13; set 2, n = 56). We removed five samples because of overlap between studies. Overall, we removed 106 samples from set 1 and 56 samples from set 2. We also removed 187 AIMs that either had low call rates (<85%) or did not pass the different filters we applied to the data before analysis, which include a test of plausibility of parental allele frequencies, a measure of Hardy-Weinberg equilibrium with special attention to excess heterozygosity, and a linkage disequilibrium test (25). For quality controls, eight duplicate pairs were analyzed in set 1, and eight duplicate pairs plus eight CEU HapMap trios were analyzed in set 2. The overall quality control concordance rate was >99.9% for both SNP panels. The final data set consisted of 1,484 invasive breast cancer cases (593 from set 1 and 891 from set 2) and 2,240 AIMs, with 645 SNPs overlapping between the two sets. The final average number of AIMs per individual used in the analysis was 1,370.

Data Analysis

Ancestry Estimation. We used the ANCESTRYMAP software (26) as the central engine of the analysis. ANCESTRYMAP calculates the percentage of ancestry for each individual in the study. These estimates are reported in Supplementary Table S2 along with the standard deviations.

Association between Global Ancestry and Tumor Characteristics. We tested the association between proportion of global individual European ancestry (values range from 0 to 1) and ER, ER/PR status, stage [localized versus non-localized (non–localized tumors includes those with regional extension only, regional nodes only, regional extension and nodes, and remote)], and grade (1 and 2 versus 3) using logistic regression models run with the STATA statistical package. Reported odds ratios (OR) refer to the difference in risk associated with a change in European ancestry proportion from 0 to 1. Age at diagnosis and study were included in the basic models as covariates. The adjusted models also included the following covariates: age at first full-term pregnancy and number of full-term pregnancies (0, no pregnancies; 1, one or two children at age less than 21; 2, one or two children at age 21 or older; 3, three or more children at age less than 21; and 4, three or more children at age 21 or older—categorical), age at menarche (1, ≤12; 2, 13-14; 3, ≥15—categorical), body mass index (BMI; continuous), family history of breast cancer in first-degree relative (0, no; 1, yes—categorical), hormone replacement therapy, and menopausal status (0, premenopausal and no current hormone replacement therapy; 1, postmenopausal and no current hormone replacement therapy; 2, postmenopausal and current hormone replacement therapy—categorical).

Association between Locus-Specific Ancestry and Breast Cancer or Tumor Characteristics. The Logarithm (base 10) of the odds score for association is defined as the log of the likelihood ratio of the data under a disease locus model versus a no-disease locus model. The ANCESTRYMAP software uses Bayesian statistics and thus requires specification of a prior distribution on risk models before carrying out the analysis. We carried out the analysis assuming a prior distribution for ancestry risk that tested both for loci associated with increased risk due to European ancestry, and increased risk due to African ancestry. For all phenotypes (all cases, ER status, ER/PR combined status, ER/grade combined status, ER/age combined status), and stages (localized versus non-localized), we ran a prior distribution considering equally likely models of 0.5, 0.6, 0.7, 0.8, 1.3, 1.5, 1.7, and 2.0-fold increased risk for European ancestry. The ANCESTRYMAP program calculates a log factor for association at equally spaced points in the genome. A local score of 5, for example, means that the data at that locus are 10^5 = 100,000 times more likely under an appropriately weighted average of the disease models, than under the null model. We followed the criteria used by Deo et al. (24) of a high threshold of >5 to be considered genome-wide significant. The frequencies of the typed SNPs in the ancestral populations were estimated based on data from European Americans and West African controls from previous studies (16, 24, 27).

Construction of Exclusion Map. To obtain credible intervals for increased risk due to African or European ancestry across the genome, we modified the procedure described elsewhere (24). ANCESTRYMAP was run for each of the three case definitions (ER+ only, ER− only, and all cases) using 85 independent disease risk models (0.30, 0.32, 0.34, 0.36, …, 1.94, 1.96, and 1.98-fold increased risk due to one European allele). We evaluated LOD scores at equally spaced points across the genome and searched for the maximum likelihood risk model at each of these points. This allowed the computation of 99.99% credible intervals for increased risk due to African (or European) ancestry by a likelihood ratio test, with the interval including all risk models for which the $\log_{10}$ of the likelihood of the disease model was within 3.275 of the maximum. Assuming 500 independent loci in the genome, these correspond to 95% genome-wide credible intervals by the Sidak correction for multiple hypothesis testing.

Results

Descriptive and tumor characteristics for cases in each of the six studies as well as for the combined sample of 1,484

[15] http://www.illumina.com/downloads/AfricanAmericanAdmixture_DataSheet.pdf

women are summarized in Table 1. The mean age at diagnosis of all cases was 54 years (range, 22-83). The average percentage of European ancestry over all cases was 23% (range, 1-98) and was relatively homogeneous among studies. The Women's Circle of Health Study had the lowest average percentage of European ancestry (19%) and the Multiethnic Cohort had the highest (25%). We observed 31% of individuals with ER− tumors, 53% with ER+ tumors, and 16% with missing status. ER− tumors were overrepresented among younger cases as noted in the LIFE study (42%) and the Los Angeles component of the Women's CARE study (35%), which is consistent with previous reports (28-30). Regarding tumor stage, 53% of the individuals had localized tumors, 34% were non-localized and 13% had missing data. In the LIFE and CARE studies, which included higher proportions of younger cases, only ~50% of the tumors were localized. For tumor grade, we observed a similar pattern, with a smaller proportion of lower grade tumors (grades 1 and 2) in the two studies that targeted younger women compared with the other studies. The percentage of European ancestry was significantly higher among individuals with hormone receptor–positive tumors compared with hormone receptor–negative tumors and women with localized disease compared with women with non-localized disease (Tables 1 and 2). We also observed a significantly higher percentage of European ancestry in women who were never pregnant compared with women who had one or more full-term pregnancies (Table 1).

Compared to women with ER− tumors, women with ER+ tumors had higher European ancestry [OR, 2.35; 95% confidence interval (CI), 1.06-5.20; Table 2]. This

Table 1. Sample and tumor characteristics for 1,484 African American women with breast cancer

	SFBABCS	BCFR	CARE	LIFE	MEC	WCHS	Total	EA % (SD)	*P**
n	185	304	372	110	409	104	1,484	23 (15)	
Age mean (SD)	55.2 (11.7)	50.4 (9.3)	48.8 (7.9)	42.3 (5.3)	65.8 (9.0)	50.0 (9.5)	54.2 (11.9)		
BMI mean kg/m^2 (SD)	30.4 (5.9)	30.3 (6.7)	27.6 (6.1)	29.0 (6.9)	29.1 (6.1)	30.4 (6.8)	29.2 (6.4)		
FHBC†									
Percent with FHBC	15	31	11	15	20	17	19	24 (17)	0.57
Percent without FHBC	85	69	84	79	72	83	77	23 (15)	
Age at first full-term pregnancy									
Percent no pregnancies	22	25	13	25	15	8	18	25 (17)	0.03‡
Percent <20	41	37	47	41	37	43	41	22 (14)	
Percent 20-30	29	34	33	27	38	30	33	24 (16)	
Percent >30	8	4	7	6	6	11	6	20 (14)	
Age at menarche									
Percent ≤12	52	47	57	54	51	47	52	23 (16)	0.18
Percent 13-14	33	39	33	37	37	40	36	23 (15)	
Percent 15 or more	14	12	10	9	10	13	11	23 (16)	
No. of full-term pregnancies									
Percent 0	22	23	13	24	15	8	17	25 (17)	<0.01
Percent 1-2	37	44	47	41	38	51	42	23 (15)	
Percent 3-5	33	29	34	31	35	27	32	23 (15)	
Percent 6 or more	8	3	6	3	8	7	6	18 (11)	
HRT/menopause status									
Percent pre-no HRT	31	58	47	81	11	35	39	23 (15)	0.13
Percent post-no HRT	45	23	23	16	61	32	36	23 (16)	
Percent post-yes HRT	16	9	14	2	16	0	12	25 (15)	
Percent estimated EA (SD)	22 (15)	23 (15)	23 (15)	23 (15)	25 (16)	19 (18)	23 (15)		<0.01§
ER status, *n* (%)									
ER+	96 (52)	158 (52)	192 (52)	45 (41)	237 (58)	57 (55)	785 (53)	24 (16)	0.04
ER−	52 (28)	92 (30)	131 (35)	46 (42)	94 (23)	41 (39)	456 (31)	22 (14)	
PR status, *n* (%)									
PR+	86 (46)	144 (47)	153 (41)	42 (38)	168 (41)	45 (43)	638 (43)	24 (16)	<0.01
PR−	61 (33)	104 (34)	121 (33)	44 (40)	111 (27)	53 (51)	494 (33)	22 (14)	
ER/PR status, *n* (%)									
ER+PR+	78 (42)	131 (43)	128 (34)	38 (35)	152 (37)	45 (43)	572 (39)	24 (17)	<0.01
ER−PR−	44 (24)	78 (26)	92 (25)	43 (39)	77 (19)	41 (39)	375 (25)	22 (14)	
ER+PR−	17 (9)	26 (9)	28 (8)	1 (1)	34 (8)	12 (12)	118 (8)	21 (14)	
ER−PR+	8 (4)	13 (4)	23 (6)	3 (3)	15 (4)	0 (0)	62 (4)	24 (12)	
Stage, *n* (%)									
Localized	118 (64)	143 (47)	186 (50)	58 (53)	281 (69)	0 (0)	786 (53)	25 (16)	<0.01
Non-localized	61 (33)	85 (28)	183 (49)	50 (45)	124 (30)	0 (0)	503 (34)	22 (14)	
Grade, *n* (%)									
1	20 (11)	34 (11)	42 (11)	8 (7)	67 (16)	12 (11)	183 (12)	24 (15)	0.27
2	63 (34)	81 (27)	98 (26)	32 (29)	132 (32)	34 (33)	440 (30)	24 (16)	
3	71 (38)	121 (40)	194 (53)	61 (56)	143 (36)	51 (49)	641 (43)	23 (15)	

NOTE: Percentages within the table did not add up to 100 because of missing data.

Abbreviations: SFBABCS, San Francisco Bay Area Breast Cancer Study; BCFR, Breast Cancer Family Registry; CARE, Contraceptive and Reproductive Experiences study; LIFE, Learning the Influence of Family and the Environment study; MEC, The Multiethnic Cohort study; WCHS, Women's Circle of Health Study; HR, hormone receptor; EA, European ancestry; FHBC, family history of breast cancer.

**P* value of ANOVA (variables are unadjusted), evaluating if there is a significant difference in the percentage of European ancestry between different groups within variables. European genetic ancestry was log-transformed to approximate normality.

†In first-degree relatives.

‡For this particular test, which compared mean genetic ancestry for the different age groups at first full-term pregnancy, we restricted the analysis to women who had at least one full-term pregnancy.

§*P* value for the comparison of European genetic ancestry between studies.

Table 2. Association between tumor characteristics and proportion of global European genetic ancestry (values of European ancestry range from 0 to 1)

	OR (95% CI)	*P*
ER+ vs. ER− status (*n* = 1,241)*,†	2.35 (1.06-5.20)	0.034
ER+ vs. ER− status adjusted‡	2.06 (0.90-4.71)	0.087
ER+PR+ vs. ER−PR− status (*n* = 947)†	4.73 (1.56-14.33)	0.006
ER+PR+ vs. ER−PR− status adjusted‡	2.84 (1.13-7.14)	0.026
Stage (localized vs. non-localized, *n* = 1,289)†	2.89 (1.22-6.81)	0.015
Stage adjusted§	2.65 (1.11-6.35)	0.029
Grade (1 and 2 vs. 3, *n* = 1,264)†	1.60 (0.77-3.32)	0.205
Grade adjusted§	1.21 (0.48-3.08)	0.687

*ER+ coded as 1 and ER− coded as 0.
†Adjusted for age and study.
‡Adjusted for number of full-term pregnancies, age at first full-term pregnancy, hormone replacement therapy use, menopausal status, BMI, age, study, age at menarche, and family history of breast cancer.
§Adjusted for number of full-term pregnancies, age at first full-term pregnancy, hormone replacement therapy use, menopausal status, BMI, age, study, age at menarche, family history of breast cancer, and estrogen receptor status.

trend was observed both in cases with localized and non–localized tumors (localized: OR, 1.60; $P = 0.39$, $n = 641$; non-localized: OR, 2.08; $P = 0.30$, $n = 429$). For ER+PR+ (versus ER−PR−) tumors the association between European ancestry and positive receptor status became stronger (OR, 4.73; 95% CI, 1.56-14.33). We adjusted the models to include factors that have been found to correlate with hormone receptor status (i.e., number of full-term pregnancies, age at first full-term pregnancy, hormone replacement therapy, menopausal status, age at menarche, BMI, and family history of breast cancer). In the adjusted model, ER status alone was no longer significantly associated with ancestry (OR, 2.06; 95% CI, 0.90-4.71). The ER+PR+ versus ER−PR− analysis showed a significant ancestry effect. The OR of the unadjusted model was 4.73 (95% CI, 1.56-14.33; $P < 0.01$). After we adjusted for potential confounders, the effect of ancestry was reduced but remained statistically significant (OR, 2.84; 95% CI, 1.13-7.14; $P = 0.026$). Among the factors included in the adjusted model, the number of full-term pregnancies had the strongest effect, with nulliparous women being more likely to have ER+PR+ tumors compared with women who have one or more children (OR for being ER+PR+ if woman has one or more children: 0.40; 95% CI, 0.26-0.60; $P < 0.01$). We observed an association between European ancestry and disease stage (localized versus non-localized), with higher European ancestry among women with localized tumors (multivariate adjusted OR, 2.65; 95% CI, 1.11-6.35) compared with women with non-localized disease. We did not find a significant relationship between tumor grade and European ancestry (Table 2).

Admixture Mapping Does Not Show Significant or Suggestive Results Either for Breast Cancer Risk or for Tumor Characteristics. We next conducted a series of genome-wide admixture scans evaluating a number of breast cancer phenotypes (as described in Materials and Methods) among 1,484 African American women with breast cancer and 1,370 AIMs per subject, on average. The data were analyzed using an affected-only statistic, which calculates the likelihood of association based on an estimate of the ancestry at a particular location relative to the overall average ancestry of the individual's genome.

No genome-wide statistically significant association was observed between European or African ancestry and breast cancer at any specific locus (Table 3). The largest LOD score genome-wide was 2.9 (we set a threshold of >5 for significance; ref. 24) on chromosome X and 2.4 on chromosome 10 (in both cases, the African allele was associated with increased risk).

A series of analyses looking at hormone receptor status and at hormone receptor status and grade combined (Table 3) were not significant. Stratifying the analyses by age did not significantly alter the results. Case to case analyses were done comparing women with tumors that were hormone receptor–negative to those with hormone receptor–positive tumors as well as women with localized tumors versus non–localized tumors. The differences in locus-specific ancestry were not significant.

Analysis of Known Breast Cancer Risk Loci. We also searched for ancestry associations within regions that have previously been reported to be associated with breast cancer risk in other populations. Four genome-wide scans have been reported to date; all of them have been conducted in populations of European or Asian ancestry. The different regions that were found to be associated with risk were 4p14, 6q22, 7q22, 10q26, 5q11, 16q12, 11p15, 8q24, 2p24, 5p12, and 2q35 (31-36). Many of these regions have also been more strongly associated with ER+ status in Europeans (37). We found a weak deviation towards higher African ancestry within the 10q26 region compared with the rest of the chromosome; this region includes the *FGFR2* gene. The *FGFR2* gene has been repeatedly identified as a breast cancer susceptibility locus by genome-wide association studies (31, 33-35), and has also recently been fine-mapped to identify specific variants (38).

Table 3. Admixture mapping whole genome scan LOD scores for 1,484 African American women with breast cancer

	Cases	ER+	ER−	ER+PR+	ER−PR−	ER+ (grade 1 and 2)	ER− (grade 3)	ER+ PR+ (grade 1 and 2)	ER−PR− (grade 3)	RA
n	1,484	785	456	572	375	462	334	331	286	
Ch 3p24	0.73	**2.86**	0.15	**2.18**	0.1	1.35	0.23	0.89	−0.12	A
Ch 5p15	0.43	0.95	1.02	0.72	**1.5**	**1.37**	1.24	0.84	**1.65**	A
Ch 10q26	**2.39**	**2.41**	**1.86**	1.56	1.06	0.83	1.11	1.09	1.15	A
Ch 18q21	−0.77	1.38	−0.34	**2.22**	−0.33	0.34	0.22	1.29	−0.19	E
Ch Xp22	**2.94**	**2.57**	0.73	1.66	0.89	0.93	**1.69**	**1.54**	0.54	A

NOTE: The best LOD scores, or scores higher than 2, for the different admixture mapping whole genome scans are in boldface. Results are presented only for chromosomes that included the highest scores in a particular scan.
Abbreviations: RA, risk allele; A, African; E, European.

Table 4. Proportion of genome excluded as contributing to differential risk for all affected individuals and for ER+ and ER− phenotypes, comparing African and European ancestries

African*	Percentage of genome excluded†			European*	Percentage of genome excluded†		
	ER+	ER−	All		ER+	ER−	All
1.0‡	0.01	0.01	0.01	1.0	0.01	0.01	0.01
1.1	1	0.01	2	1.1	3	0.2	5
1.2	8	1	28	1.2	13	3	32
1.3	31	9	64	1.3	39	11	73
1.4	57	26	85	1.4	70	28	98
1.5	78	48	96	1.5	92	55	100
1.6	89	66	99	1.6	98	79	100
1.7	95	78	100	1.7	100	92	100
1.8	98	87	100	1.8	100	99	100
1.9	100	92	100	1.9	100	100	100
2.0	100	95	100	2.0	100	100	100
2.1	100	97	100	2.1	100	100	100
2.2	100	99	100	2.2	100	100	100
2.3	100	99	100	2.3	100	100	100
2.4	100	100	100	2.4	100	100	100

*Factor by which African (European) ancestry increases risk at this locus compared with European (African) ancestry.
†Percentage of genome excluded as having this risk or more at $P < 0.05$ genome-wide.
‡The percentage of the genome in which the null hypothesis (relative risk due to ancestry = 1) is excluded was ~0.01% for all scenarios, as expected using a $P < 0.0001$ significance cutoff, which is the corrected 5% cutoff for genome-wide significance (assuming 500 independent loci).

Exclusion Map. We prepared an exclusion map for the three case definitions with the largest sample sizes: all cases, ER+, and ER− cases. At least 98% of the genome can be excluded as having a European effect on risk of 1.4 or more, and at least 96% can be excluded as having an African effect on risk of 1.5 or more (Table 4). The power of the ER status analysis is less than that for all cases because of the smaller sample size. In the case of ER− disease, we can exclude 87% of the genome as having an increased risk of 1.8 or higher due to African ancestry and 92% as having an increased risk of 1.7 or higher due to European ancestry. In the case of ER+ disease, we can exclude 89% of the genome as having an increased risk of 1.6 or higher associated with African ancestry and 92% as having an increased risk of 1.5 or higher associated with European ancestry (Table 4).

Discussion

The present study represents the first genome-wide admixture scan conducted in African American women with breast cancer. In this study, we did not find an association between breast cancer risk and African or European ancestry at any specific loci among all cases or within subtypes of breast cancer, at genome-wide levels of significance. We detected European ancestry to be overrepresented among women with ER+ tumors. However, adjustment for known breast cancer risk factors could explain this association. A significant association remained for ER+PR+ tumors following adjustment, which could be due to misclassification of these risk factors, other risk factors which we did not consider (e.g., alcohol consumption), or that we do not know about that do correlate with ancestry and influence tumor characteristics. At the same time, it is possible that this association is due to genetic risk factors that correlate with ancestry. We observed that nulliparity was associated with both ER+PR+ disease as well as European ancestry. The association between number of full-term pregnancies and hormone receptors status has been reported previously in African Americans and white women (29), and our data replicates these results. The association between nulliparity and ER+PR+ disease could be the result of an underlying biological mechanism or could be due to the correlation between this risk factor and other known or unknown risk factors that we did not account for. The association between European ancestry and nulliparity was also significant ($P = 0.01$) but could not completely explain the association that we observed between ancestry and ER/PR status. We also detected European ancestry to be significantly overrepresented among women with localized tumors compared with women with non–localized tumors (OR, 2.65; 95% CI, 1.11-6.35; $P = 0.029$). This association could not be explained by the known breast cancer risk factors.

The exclusion map shows that for the analysis of the ER− cases, we had reasonable power to detect an increased risk due to an African allele of 1.8 and above and an increased risk due to a European allele of 1.6 and above. Therefore, the fact that our scan did not detect any significant signal does not discard the possibility that ancestry effects of 1.7 or lower are present. The observed association between ancestry and ER/PR status supports this possibility and suggests that further analyses are needed with adequate power to detect ancestry effects on risk of 1.7 or less.

We detected a nonsignificant deviation towards higher African ancestry on chromosome 10q26 compared with the chromosomal average. This region includes the *FGFR2* gene and a common variant that is associated with increased risk of breast cancer in Asian and European populations (33, 34, 38). A recently published study investigated FGFR2 variants in African Americans, Asians, and Europeans to search for causative variants and to evaluate if the same variants were associated with risk of breast cancer in the different racial/ethnic groups (38). Based on association results, and an analysis of DNase I hypersensitive sites looking at chromatin accessibility, the conclusion was reached that two variants, rs2981578 and rs10736303, are the most likely to be causal variants. The frequency of these two variants is different in African populations compared with Europeans or Asians. The frequency of the risk allele for the variant rs2981578 is 0.93 in the HapMap African sample and 0.46 in the HapMap European samples. A similar difference was observed for rs10736303, with the risk allele having a frequency of 0.92 in Africans and 0.60 in Europeans.[16] The increase in African ancestry that we observed in the admixture mapping analysis within the 10q26 region could potentially be explained by the higher frequency of causal risk alleles in this region, which are likely to be more common in African than European populations.

There was no apparent deviation from the average chromosomal ancestry for any other region of the genome previously reported to have a risk variant. Different studies have reported associations between variants in the *FGFR2* gene and breast cancer risk, with per allele ORs that varied between 1.20 and 1.30 (33, 34, 38-40). The reported ORs for the *FGFR2* gene are among the higher reported ORs compared with those of other risk variants discovered through whole genome association studies (~1.25 compared with <1.20; ref. 39). Adding to this, the candidate variants within the *FGFR2* gene show a large allele frequency difference between Europeans and Africans. Therefore, it is likely that we did not observe any other ancestry deviations because of lack of power (we had power >80% to detect risk variants with an allele effect of 1.5 or larger; if the allele effect was ~1.2, then the allele frequency difference between the ancestral populations needed to be larger than 0.7 to achieve a power above 40%).

One limitation of this study is the sample size. Although the study included >1,400 women, ER−PR− cases are still a minority of cases, even among African Americans, and thus, we had limited power to assess associations for the different breast cancer phenotypes.

Her2 status was not available for the majority of cases because most of the cases in the different studies were recruited at a time when Her2 status was not routinely assayed for clinical testing. Therefore, we were unable to analyze ER−PR−Her2-negative breast cancer cases (i.e., "triple negatives"), an aggressive subset of tumors that has been estimated to be more common in African Americans than in European Americans (28-30, 41). Much larger studies in African populations, with available tumor specimen resources for tumor phenotyping, will be needed to evaluate the genetic contribution to the various breast cancer subtypes.

Information about ER and PR status, grade, and stage, comes from pathology reports or from the cancer registry, depending on the study. Therefore, it is likely that there were differences in how the tumors were classified. This potential misclassification could have contributed to the negative results observed. However, the frequency of the different tumor characteristics in the six studies are similar and when they differ, they do it in the expected direction given the age distribution of the women in the studies. This suggests that misclassification might not be a serious problem for these data, although caution must be taken in the interpretation of the results. Future studies involving centralized tumor marker data collection will be necessary to avoid the potential effect of misclassification in genetic epidemiology studies with multiple data sources.

The AIMs selected to infer genetic ancestry are assumed to have homogenous frequency within the African continent. Given that African Americans are likely to have a mixed ancestry from different regions of Western Africa (42), which might not share the same allele frequencies for the markers used in the present study, results must be interpreted with caution.

The clinical implications of the differences in tumor presentation of African American women with breast cancer compared with European American patients are substantial. Although the overall incidence of breast cancer is lower in African American women, the mortality rate is higher in African American women than in European American women (43). This may be in part be due to higher rates of ER− disease because hormonal treatment, either with selective estrogen receptor modifiers (tamoxifen or raloxifene) or with aromatase inhibitors, is highly effective for ER+ disease only (44). Furthermore, ER− disease often occurs in younger women who have never had screening because they are younger than the standard screening age and because screening with mammography is less sensitive among younger women (45). The high rates of ER− disease among African Americans may also have implications for breast cancer prevention. Tamoxifen and raloxifene have been shown to prevent ER+ breast cancer in primary prevention studies, and some have advocated that the medications be used in women at high risk (44, 46). In addition, aromatase inhibitors may also be useful in the prevention of breast cancer (47). However, there is no clear preventive strategy for ER− breast cancers. Identifying the causal factors that explain the difference in incidence of hormone receptor–negative tumors between European American and African American women should be a high priority.

The present admixture mapping scan in 1,484 African American women with breast cancer suggests that the difference in breast cancer risk between Europeans and African Americans is unlikely to be due to an effect of a European or African allele on risk larger than 1.7. It also excludes an effect on risk for ER+ status larger than 1.9 and for ER− status larger than 2.4. Global ancestry association results, however, show a positive association of European ancestry with stage of disease, and with ER+PR+ disease. These associations could result from population differences in nongenetic risk factors or from the effect of multiple genetic variants each with a relatively moderate contribution to the ancestry-related risk difference.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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[16] http://www.ncbi.nlm.nih.gov/sites/entrez

References

1. Ries LAG, Eisner MP, Kosary CL, et al. SEER cancer statistics review 1975–2000. Bethesda: National Cancer Institute 2003.
2. Althuis MD, Brogan DD, Coates RJ, et al. Breast cancers among very young premenopausal women (United States). Cancer Causes Control 2003;14:151–60.
3. Joslyn SA, West MM. Racial differences in breast carcinoma survival. Cancer 2000;88:114–23.
4. Fejerman L, Ziv E. Population differences in breast cancer severity. Pharmacogenomics 2008;9:323–33.
5. Chlebowski RT, Chen Z, Rohan T, et al. Ethnicity and breast cancer in the Women's Health Initiative: a unifying concept for unfavorable outcome in African American women [abstract 1008]. J Clin Oncol 2004;22.
6. Amend K, Hicks D, Ambrosone CB. Breast cancer in African-American women: differences in tumor biology from European-American women. Cancer Res 2006;66:8327–30.
7. Newman LA, Bunner S, Carolin K, et al. Ethnicity related differences in the survival of young breast carcinoma patients. Cancer 2002;95: 21–7.
8. Joslyn SA. Hormone receptors in breast cancer: racial differences in distribution and survival. Breast Cancer Res Treat 2002;73:45–59.
9. English WP, Cleveland KE, Barber WH. There is no difference in survival between African-American and white women with breast cancer. Am Surg 2002;68:594–7.
10. Chlebowski RT, Chen Z, Anderson GL, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst 2005;97:439–48.
11. Rosenberg NA, Li LM, Ward R, Pritchard JK. Informativeness of genetic markers for inference of ancestry. Am J Hum Genet 2003;73: 1402–22.
12. McKeigue PM. Mapping genes that underlie ethnic differences in disease risk: methods for detecting linkage in admixed populations, by conditioning on parental admixture. Am J Hum Genet 1998;63:241–51.
13. Collins-Schramm HE, Phillips CM, Operario DJ, et al. Ethnic-difference markers for use in mapping by admixture linkage disequilibrium. Am J Hum Genet 2002;70:737–50.
14. Smith MW, O'Brien SJ. Mapping by admixture linkage disequilibrium: advances, limitations and guidelines. Nat Rev Genet 2005;6:623–32.
15. Collins-Schramm HE, Chima B, Operario DJ, Criswell LA, Seldin MF. Markers informative for ancestry demonstrate consistent megabase-length linkage disequilibrium in the African American population. Hum Genet 2003;113:211–9.
16. Freedman ML, Haiman CA, Patterson N, et al. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad Sci U S A 2006;103:14068–73.
17. Pike MC, Kolonel LN, Henderson BE, et al. Breast cancer in a multiethnic cohort in Hawaii and Los Angeles: risk factor-adjusted incidence in Japanese equals and in Hawaiians exceeds that in whites. Cancer Epidemiol Biomarkers Prev 2002;11:795–800.
18. Kolonel LN, Henderson BE, Hankin JH, et al. A multiethnic cohort in Hawaii and Los Angeles: baseline characteristics. Am J Epidemiol 2000;151:346–57.
19. Marchbanks PA, McDonald JA, Wilson HG, et al. The NICHD Women's Contraceptive and Reproductive Experiences Study: methods and operational results. Ann Epidemiol 2002;12:213–21.
20. Ma H, Bernstein L, Ross RK, Ursin G. Hormone-related risk factors for breast cancer in women under age 50 years by estrogen and progesterone receptor status: results from a case-control and a case-case comparison. Breast Cancer Res 2006;8:R39.
21. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multiethnic population. Am J Epidemiol 2007;166:1409–19.
22. John EM, Horn-Ross PL, Koo J. Lifetime physical activity and breast cancer risk in a multiethnic population: the San Francisco Bay Area Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2003;12: 1143–52.
23. John EM, Hopper JL, Beck JC, et al. The Breast Cancer Family Registry: an infrastructure for cooperative multinational, interdisciplinary and translational studies of the genetic epidemiology of breast cancer. Breast Cancer Res 2004;6:R375–89.
24. Deo RC, Patterson N, Tandon A, et al. A high-density admixture scan in 1,670 African Americans with hypertension. PLoS Genet 2007;3:e196.
25. Reich D, Patterson N, De Jager PL, et al. A whole-genome admixture scan finds a candidate locus for multiple sclerosis susceptibility. Nat Genet 2005;37:1113–8.
26. Patterson N, Hattangadi N, Lane B, et al. Methods for high-density admixture mapping of disease genes. Am J Hum Genet 2004; 74:979–1000.
27. Smith MW, Patterson N, Lautenberger JA, et al. A high-density admixture map for disease gene discovery in African Americans. Am J Hum Genet 2004;74:1001–13.
28. Carey LA, Perou CM, Livasy CA, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295: 2492–502.
29. Millikan RC, Newman B, Tse CK, et al. Epidemiology of basal-like breast cancer. Breast Cancer Res Treat 2008;109:123–39.
30. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. Cancer 2007;109:1721–8.
31. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosome 5p12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2008;40:703–6.
32. Stacey SN, Manolescu A, Sulem P, et al. Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor-positive breast cancer. Nat Genet 2007;39:865–9.
33. Hunter DJ, Kraft P, Jacobs KB, et al. A genome-wide association study identifies alleles in FGFR2 associated with risk of sporadic postmenopausal breast cancer. Nat Genet 2007;39:870–4.
34. Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007; 447:1087–93.
35. Gold B, Kirchhoff T, Stefanov S, et al. Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33. Proc Natl Acad Sci U S A 2008;105:4340–5.
36. Ghoussaini M, Song H, Koessler T, et al. Multiple loci with different cancer specificities within the 8q24 gene desert. J Natl Cancer Inst 2008;100:962–6.
37. Garcia-Closas M, Hall P, Nevanlinna H, et al. Heterogeneity of breast cancer associations with five susceptibility loci by clinical and pathological characteristics. PLoS Genet 2008;4:e1000054.
38. Udler MS, Meyer KB, Pooley KA, et al. FGFR2 variants and breast cancer risk: fine-scale mapping using African American studies and analysis of chromatin conformation. Hum Mol Genet 2009; 18:1692–703.
39. Easton DF, Eeles RA. Genome-wide association studies in cancer. Hum Mol Genet 2008;17:R109–15.
40. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). Nat Genet 2009;41:579–84.
41. Olopade OI, Ikpatt FO, Dignam JJ, et al. "Intrinsic Gene Expression" subtypes correlated with grade and morphometric parameters reveal a high proportion of aggressive basal-like tumors among black women of African ancestry [abstract 9509]. J Clin Oncol 2004;22.
42. Tishkoff SA, Reed FA, Friedlaender FR, et al. The genetic structure and history of Africans and African Americans. Science 2009;324:1035–44.
43. Ademuyiwa FO, Olopade OI. Racial differences in genetic factors associated with breast cancer. Cancer Metastasis Rev 2003;22:47–53.
44. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371–88.
45. Cunningham JE, Butler WM. Racial disparities in female breast cancer in South Carolina: clinical evidence for a biological basis. Breast Cancer Res Treat 2004;88:161–76.
46. Cummings SR, Eckert S, Krueger KA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189–97.
47. Dunn BK, Wickerham DL, Ford L. Prevention of hormone-related cancers: breast cancer. J Clin Oncol 2005;23:357–67.

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Brief Communication

Traumatic stress symptoms and breast cancer: The role of childhood abuse☆

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ABSTRACT

Objective: The present study investigated relations between reported childhood abuse and recent traumatic stress symptoms in women newly diagnosed with breast cancer ($n = 330$).
Methods: As part of a larger ongoing study, patients from eight public and private hospitals were referred by their physicians and completed the Childhood Trauma Questionnaire (CTQ), and the Impact of Events Scale-breast cancer (IES), which measured breast cancer-related intrusive and avoidant symptoms.
Results: Emotional abuse, physical abuse, and sexual abuse were correlated with intrusive symptoms. Cancer-related avoidant symptoms approached significance in their relation to emotional and sexual abuse. Multivariate analysis, controlling for age and time since diagnosis, revealed that childhood emotional abuse was an independent predictor of breast cancer-related intrusive symptoms, but that childhood physical abuse and sexual abuse were not significant predictors.
Conclusions: Childhood emotional, physical, and sexual abuse were associated with breast cancer-related intrusive symptoms. Emotional abuse uniquely predicted intrusive symptoms after controlling for other predictors. Results suggest that a cancer diagnosis may trigger cognitive and emotional responses that relate to patients' prior trauma experiences.
Practice implications: Physicians and psychologists treating women with breast cancer should be aware that a history of childhood abuse may exacerbate patients' cancer-related intrusive symptoms. Interventions for women affected by both childhood abuse and breast cancer may be most effective when they address both stressors and associated emotional responses. Findings highlight the importance of additional research to explore links between prior trauma and distress following a cancer diagnosis stress.

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Introduction

Breast cancer is the most commonly diagnosed cancer and the second-leading cause of cancer deaths among women in the United States (Ries et al., 2007). In addition to substantial physical challenges, many women with breast cancer experience depression, anxiety, and posttraumatic intrusive and avoidant symptoms (e.g., Koopman et al., 2002). Prospective studies indicate that breast cancer-related intrusive symptoms at the time of diagnosis are predictive of long-term distress, including anxiety and depression (e.g., Epping-Jordan et al., 1999). It is less clear, however, if childhood abuse increases vulnerability to current cancer-related traumatic stress symptoms. The present study seeks to address this issue.

Psychosocial variables such as a younger age at diagnosis, lower income, and a more recent breast cancer diagnosis are associated with higher levels of traumatic stress symptoms, including intrusive and avoidant symptoms (e.g., Koopman et al., 2002). Intrusive symptoms include unwanted cancer-related thoughts, images, emotions, and dreams, whereas avoidant symptoms constitute attempts to avoid cancer-related thoughts, feelings, or reminders. A small body of research indicates that women with prior trauma experiences report more severe breast cancer-related traumatic stress symptoms. Breast cancer-related intrusive and avoidant symptoms have been associated with the number of past traumas (Andrykowski, Cordova, McGrath, Sloan, & Kenady, 2000), having parents who survived the Holocaust (Baider et al., 2000; Baider, Goldsweig, Ever Hadani, & Peretz, 2006), and with lifetime exposure to past traumas and current stressors (Green et al., 2000). Only one study (Salmon et al., 2006) examined the specific relation between breast cancer-related traumatic stress symptoms and childhood abuse. Salmon et al. assessed abuse using five self-report questions culled from published surveys, and reported that sexual and emotional abuse were related to levels of general mental distress, whereas physical and emotional abuse were associated with traumatic stress symptoms.

A history of childhood abuse is generally quite prevalent among health care populations. One study of 292 adults in a primary care setting found that 44% reported childhood abuse (Gould et al., 1994). Felitti et al. (1998) reported prevalence rates of 11.1% for emotional abuse, 10.8% for physical abuse, and 22.0% for sexual abuse among 9508 patients in a large HMO, as well as a dose–response relationship between the number of childhood traumas and the likelihood of adult cancer diagnoses. An extensive literature, including prospective studies, demonstrates strong associations between childhood abuse and adult physical and mental health difficulties (e.g., Horwitz, Widom, McLaughlin, & White, 2001; Kendall-Tackett, 2002; Silverman, Reinherz, & Giaconia, 1996). Emotional abuse may comprise a basis for all forms of abuse and neglect (e.g., Hart & Brassard, 1987; Schore, 2001), and recent empirical evidence indicates that emotional abuse is related to psychological difficulties to a greater extent than are other abuse subtypes (e.g., Gibb, Chelminski, & Zimmerman, 2007; Spertus, Yehuda, Wong, Halligan, & Seremetis, 2003; Teicher, Samson, Polcari, & McGreenery, 2006).

Researchers have proposed several possible mechanisms for the dysregulations in affect, cognitions, and neurobiological systems observed in survivors of childhood abuse and other trauma (e.g., Bremner, 2003; Brewin & Holmes, 2003; Briere, 2002). For instance, Briere (2002) proposes that conditioned emotional responses occur in response to abuse-related stimuli, are inculcated during repeated abuse, and may generalize to subsequent stressors. Brewin and Holmes (2003) describe three recent theoretical approaches to posttraumatic responses that emphasize components such as encoding, appraisal, beliefs, and cognitive styles. Emotional processing theory (Foa & Rothbaum, 1998), dual representation theory (Brewin, Dalgleish, & Joseph, 1996), and Ehlers and Clark (2000) cognitive theory provide accounts of psychological processes that are each consistent with a wide scope of empirical data, but differ with respect to the pathways proposed. Other contributions accentuate psychobiological responses to trauma, including sympathetic nervous system hyperreactivity and abnormalities in neurotransmitter and neuroendricine activity (e.g., Friedman & McEwan, 2004). Bremner (2003) hypothesizes that long-term alterations in brain regions and neurochemical systems may contribute to enduring posttraumatic symptoms in childhood abuse survivors. Although the specific mechanisms through which childhood trauma relates to adult psychological difficulties have yet to be established, research indicates that a history of childhood abuse is associated with increased posttraumatic stress symptoms and maladaptive coping in response to subsequent stressors (Bremner, Southwick, Johnson, Yehuda, & Charney, 1993; Leitenberg, Gibson, & Novy, 2004). These models and data suggest that childhood abuse would be positively associated with levels of traumatic stress symptoms following a cancer diagnosis.

The current study explored the relations among childhood abuse and cancer-related intrusive and avoidant symptoms in newly diagnosed breast cancer patients using validated measures with strong psychometric properties. The study examined the hypothesis that childhood abuse, particularly emotional abuse, would be associated with these patients' levels of cancer-related intrusive and avoidant symptoms.

Method

Participants

Participants for the present study were 350 women who were recruited as part of a larger, ongoing molecular epidemiologic case–control study on reproductive, hormonal, and behavioral factors in women with breast cancer. Two hundred women (61%) were African American, and 130 (39%) were White/European American. Forty-nine women (15%) reported 11 or fewer years of education, 73 (22%) reported having received a high school diploma, and 208 (63%) reported additional education. Ninety-seven women (32%) reported an income of below $20,000 per year; 82 women (27%) reported earning between $20,000 and $49,999 per year; and 128 women (41%) reported an income of over $50,000 per year. Eighty-four women (25%) reported that they were currently receiving medical treatment, whereas 203 women (62%) indicated that they were not. Participants had undergone a range of medical treatments, including chemotherapy ($n = 119$; 36%), radiation ($n = 100$; 30%), a combination of radiation and chemotherapy ($n = 50$; 15%), surgery ($n = 25$; 8%), or other treatment ($n = 36$; 11%). Forty-three women (13%) did not provide their treatment status, and 147 women (45%) did not supply information regarding the type of medical treatment they had received.

Study participants were recruited from public and private hospitals in the New York metropolitan area. Inclusion criteria for the larger study included female sex, a breast cancer diagnosis within the previous 9 months, no history of previous cancers (excluding non-melanoma skin cancer), a Black/African American or White/European American racial background, and English proficiency. The present sample included all patients with complete data for age, race, income, and education ($n = 330$).

Materials

An in-person interview was used to collect data on self-reported age, race, income, education, date of cancer diagnosis, and current medical treatment (e.g., chemotherapy, radiation, or medications). Participants also completed the two self-report measures described below.

The Impact of Events Scale (Horowitz, Wilner, & Alvarez, 1979) was used to measure traumatic stress symptoms related to breast cancer over the previous 2 weeks. The IES is the most commonly used instrument for assessing traumatic stress symptoms among cancer patients (Gurevich, Devins, & Rodin, 2002), and has well-established content, construct, convergent, and clinical validities. The scale uses a 4-point Likert scale (0 = not at all; 1 = rarely; 3 = sometimes; 5 = often) and contains two subscales: a 7-item scale of intrusive thoughts, feelings, images and nightmares, and an 8-item scale of cognitive and behavioral avoidance of stimuli related to a stressor (in this case, breast cancer). Items were presented to participants visually as a categorical scale with both verbal descriptions and numeric responses. Item scores are totaled and averaged for each subscale. Distributions for the IES had acceptable levels of skewness and kurtosis (±1.0). In the present sample, $\alpha = .86$ for intrusive symptoms and .83 for avoidant symptoms.

The Child Trauma Questionnaire (Bernstein et al., 2003) was used to assess childhood abuse. The 28-item CTQ contains emotional, physical, and sexual abuse subscales, and has established validity and consistency (Bernstein et al., 2003). Scores are continuous and represent the amount of childhood abuse experiences that participants report. Respondents indicated the extent of their experiences before puberty for each item using a Likert scale (1 = never; 5 = very often), which are then summed for each subscale. Participants' questionnaires included both verbal descriptions and numeric responses for the measure's Likert scale. For this sample, $\alpha = .84$ for emotional abuse, .77 for physical abuse, and .88 for sexual abuse.

Procedure

Women who met eligibility criteria were identified at eight hospitals in the New York metropolitan region and in eastern New Jersey. After physician consent, patients were invited to participate. All participants signed informed consent and HIPAA forms and received $25.00. After a detailed interview, participants completed self-report measures without assistance and in privacy. The project was approved by the Institutional Review Boards of the Mount Sinai School of Medicine, the New Jersey Department of Health, and each participating hospital.

Data analysis

For individuals with missing data on the CTQ or any other continuous variable, a state of the art procedure for missing data was used (PROC MI and PROC MIANALYZE in SAS) with the recommended 5 cycles of imputation (Schafer & Graham, 2002). This procedure imputed data for 3 CTQ sexual abuse items that were missing from 213 women due to a clerical printing error. For these data, multiple imputation was especially appropriate because the probability of missing data was unrelated to their values or to other variables (Allison, 2002). Descriptive statistics and Pearson correlations were then generated. Simultaneous multiple regression models (PROC REG in SAS) were run to examine unique relationships between CTQ and IES scores, after controlling for age and time since diagnosis. To confirm the results, the models were rerun using only data from women with no missing data ($n = 119$).

Results

Descriptive statistics and intercorrelations for the study variables are presented in Table 1. Table 1 presents a correlation matrix for variables correlated with childhood abuse measures and with intrusive and avoidant symptoms. Emotional abuse was associated with intrusive symptoms ($r = .23$, $p < .001$). Physical abuse was correlated with intrusive symptoms at the level of $r = .13$ ($p < .05$), and sexual abuse was correlated with intrusive symptoms at the level of $r = .12$ ($p < .05$). Emotional abuse was related to avoidant symptoms at the level of $r = .10$ ($p = .06$). The relation between sexual abuse and avoidant symptoms also approached significance ($r = .10$, $p = .07$); however, the relation between physical abuse and avoidant symptoms did not ($r = .07$, $p = .23$). Age was significantly negatively related to intrusive symptoms ($r = -.21$, $p = .001$). The correlation between the number of days since diagnosis and intrusive symptoms approached significance ($r = -.11$, $p = .06$). Results indicated that

Table 1
Means, standard deviations, and intercorrelations for variables related to IES scores ($n = 330$).

Variable	Mean	SD	1	2	3	4	5	6	7	8
1. Age	50.68	9.86								
2. Days since diagnosis	211.22	137.30	.02							
3. Race (see note)	–	–	.11*	.08	–					
4. Income (see note)	–	–	.01	.10	.55***					
5. Emotional abuse	7.85	4.04	.00	.03	.15**	.00				
6. Physical abuse	6.65	2.94	−.04	.00	−.13*	−.09	.58***			
7. Sexual abuse	6.34	3.16	−.11*	.02	−.05	−.07	.44***	.50***		
8. IES intrusion	1.78	1.27	−.21**	−.11	−.08	−.10	.23***	.13*	.12*	
9. IES avoidance	1.88	1.23	−.09	−.08	−.16**	−.16**	.10	.07	.10	.60***

Note: Race was coded as 0 = Black/African/African American and 1 = European American/White. Correlations that used race were explored using point biserial correlations. Annual income before taxes for the last year was measured with an ordinal scale where 1 = less than \$15,000; 2 = \$15,000–19,999; 3 = \$20,000–24,999; 4 = \$25,000–34,999; 5 = \$35,000–49,000; 6 = \$50,000–69,000; 7 = \$70,000–89,999; 8 = \$90,000 or more. Education and current treatment were not related ($p < .10$) to IES scores.

* $p < .05$.
** $p < .01$.
*** $p < .001$.

Table 2
Summary of simultaneous multivariate regression model for variables predicting IES intrusive symptoms ($n = 330$).

Variable	Adjusted	R^2	*F*	*df*	*p*	*b*	*t*	*p*
Model: Predicting IES intrusion	.10	8.04	329	<.0001				
Age						.007	−3.94	<.0001
Days since diagnosis						.0005	−2.08	.04
Emotional abuse						.02	3.85	.002
Physical abuse						.02	−.46	.65
Sexual abuse						.02	.11	.87

race and income were associated with avoidant symptoms, with African American women and women with lower incomes reporting higher levels of avoidant symptoms ($r = -.16$, $p < .05$ for both correlations).

To determine if childhood abuse was significantly related to intrusive symptoms after controlling for the potentially confounding variables of age and time since diagnosis, a simultaneous multiple regression analyses was conducted. Because no abuse subscales were related to avoidant symptoms at levels of $p < .05$, a model was constructed to predict intrusive symptoms only (Table 2). The model indicated that intrusive symptoms were independently negatively related to age and days since diagnosis, and positively related to emotional abuse. When the model was rerun using only participants with complete data, emotional abuse remained a significant predictor of intrusive symptoms [$t(118) = 4.04$, $p = < .0001$].

Discussion

In this study, childhood abuse was associated with breast cancer-related intrusive symptoms among women with recently diagnosed breast cancer. Although all three abuse subtypes were related to intrusive symptoms, emotional abuse uniquely predicted intrusive symptoms after controlling for other predictors. These data constitute the first report of an association between any type of childhood abuse assessed with a validated measure and breast cancer-related intrusive symptoms. These findings are congruent with previous research (e.g., Gibb et al., 2007; Spertus et al., 2003) that identifies emotional abuse as especially predictive of adult emotional difficulties. These data may reflect the continuing cognitive and emotional schemas, hypervigilance, dysregulated stress responses, and altered neurological systems observed in survivors of childhood abuse (Bremner, 2003; Briere, 2002; De Bellis, 2001; Schore, 2001). A cancer diagnosis may trigger negative cognitions and emotions that are consistent with patients' prior trauma experiences.

As in previous studies (e.g., Green et al., 2000; Koopman et al., 2002), younger women with breast cancer reported more severe psychological symptoms. Psychological symptoms were not related to patients' current treatment status or type of treatment received, a result consistent with other data (e.g., Green et al., 2000). IES scores for this sample were comparable to other reports of women recently diagnosed with breast cancer (e.g., Epping-Jordan et al., 1999). CTQ subscale scores were somewhat lower than reports of abuse among substance abusing or psychiatric participants (Bernstein et al., 2003), and similar to other samples (e.g., Thombs et al., 2007). The finding that avoidant symptoms were related to intrusive symptoms, but not to childhood abuse, is somewhat surprising given previous reports of associations between childhood abuse and avoidant symptoms (e.g., Stovall-McClough & Cloitre, 2006; Yoshihama & Horrocks, 2002). The present results are, however, consistent with conceptualizations and research that regard avoidant symptoms as attempts to defend oneself against intrusive symptoms, rather than as resulting directly from trauma (McFarlane, 1992). Avoidant symptoms appear to predict and perpetuate subsequent intrusive symptoms in cancer and other medical populations (Lawrence, Fauerbach, & Munster, 1996; Manne, Glassman, & Du Hamel, 2000). The results demonstrate relations among race, income, abuse subtype, and avoidant symptoms that merit further investigation in future studies.

The clinical implications of this study include the potential to screen and provide services to newly diagnosed cancer patients with a history of childhood abuse. Just as physicians assess preexisting conditions, psychologists should consider prior vulnerabilities that may exacerbate current stressors. While many breast cancer patients have low levels of distress and may not need psychological interventions, those who report higher levels of childhood abuse have more severe psychological symptoms. Treating this population may prove beneficial, as trauma-focused interventions appear to be more effective than other treatments for survivors of trauma (e.g., Bisson et al., 2007), and because health care costs are greater for survivors of abuse, even after controlling for chronic diseases (e.g., Walker et al., 1999). The findings also underscore the need for further efforts in child abuse prevention and in training health care professionals regarding the profound, life-long effects of childhood abuse (see Courtois, 2002).

The study had several limitations. The project was cross-sectional, and only included patients with European and African backgrounds. Other limitations included some missing data, particularly on the sexual abuse subscale, and the unavailability of data regarding the type and stage of breast cancer. Several of the correlations reported were quite small, and should be interpreted with caution. The overall variance in IES intrusive symptoms was relatively small. While emotional abuse was a significant predictor of IES intrusive symptoms in the multivariate analysis, age and days since diagnosis also made significant contributions. The study used retrospective self-report data to gather information about abuse experiences, a method with both advantages and disadvantages (Kendall-Tackett & Becker-Blease, 2004). Studies indicate that survivors' perceptions of childhood abuse differ from those of researchers, who are more likely to view behaviors as abusive (e.g., Knutson & Selner, 1994; Silvern, Waelde, Baughan, Karyl, & Kaersvang, 2000). Retrospective data may contain false negative reports (e.g., Fergusson, Horwood, & Woodward, 2000), whereas false positive reports are rare (e.g., Hardt & Rutter, 2004). Although retrospective data may include multiple sources of error, adults appear "generally accurate" (Brewin, Andrews, & Gotlib, 1993, p. 87) regarding factual childhood details. The study did not assess adolescent or adult trauma, which may contribute to patients' psychological symptoms.

This report forms a basis for future work examining psychological symptoms in survivors of childhood abuse and breast cancer. Research on stress and breast cancer has concentrated on current circumstances and recent life events (Delahanty & Baum, 2001). Future research should address the limitations of the present study, investigate additional ways childhood abuse relates to coping with breast cancer and other diseases, and explore facets of emotional processing such as emotion regulation that may mediate relations between childhood abuse and current traumatic stress symptoms. Finally, interventions with women impacted by both abuse and cancer may provide information regarding effective support for this population.

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References

Allison, P. D. (2002). *Missing data*. Thousand Oaks, CA: Sage.

Andrykowski, M. A., Cordova, M. J., McGrath, P. C., Sloan, D. A., & Kenady, D. E. (2000). Stability and change in posttraumatic stress disorder symptoms following breast cancer treatment: A 1-year follow-up. *Psycho-oncology*, *9*(1), 69–78.

Baider, L., Peretz, T., Ever Hadani, P. E., Perry, S., Avramov, R., & De-Nour, A. K. (2000). Transmission of response to trauma? Second-generation Holocaust survivors' reaction to cancer. *American Journal of Psychiatry*, *157*(6), 904–910.

Baider, L., Goldsweig, G., Ever Hadani, P., & Peretz, T. (2006). Psychological distress and coping in breast cancer patients and healthy women whose parents survived the Holocaust. *Psycho-oncology*, *15*(7), 635–646.

Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., Stokes, J., Handelsman, L., Medrano, M., Desmond, D., & Zule, W. (2003). Development and validation of a brief screening version of the Child Trauma Questionnaire. *Child Abuse & Neglect*, *27*, 169–190.

Bisson, J. I., Ehlers, A., Matthews, R., Pilling, S., Richards, D., & Turner, S. (2007). Psychological treatments for chronic post-traumatic stress disorder. Systematic review and meta-analysis. *British Journal of Psychiatry*, *190*, 97–104.

Bremner, J. D. (2003). Long-term effects of childhood abuse on brain and neurobiology. *Child and Adolescent Psychiatric Clinics of North America*, *12*(2), 271–292.

Bremner, J. D., Southwick, S. M., Johnson, D. R., Yehuda, R., & Charney, D. (1993). Childhood physical abuse in combat-related posttraumatic stress disorder. *American Journal of Psychiatry*, *150*, 235–239.

Brewin, C. R., Andrews, B., & Gotlib, I. H. (1993). Psychopathology and early experience: A reappraisal of retrospective reports. *Psychological Bulletin*, *113*, 82–98.

Brewin, C. R., Dalgleish, T., & Joseph, S. (1996). A dual-representation theory of post-traumatic stress disorder. *Psychological Review*, 670–686.

Brewin, C. R., & Holmes, E. A. (2003). Psychological theories of posttraumatic stress disorder. *Clinical Psychology Review*, *23*, 339–376.

Briere, J. (2002). Treating adult survivors of severe childhood abuse and neglect: Further development of an integrative model. In J. E. B. Meyers, L. Berliner, J. Briere, C. T. Hendrix, T. Reid, & C. Jenny (Eds.), *The APSAC handbook on child maltreatment* (2nd ed., pp. 175–203). Thousand Oaks, CA: Sage.

Courtois, C. A. (2002). Traumatic stress studies: The need for curricula inclusion. *Journal of Trauma Practice*, *1*, 33–58.

De Bellis, M. D. (2001). Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. *Development and Psychopathology*, *13*(3), 539–564.

Delahanty, D. L., & Baum, A. (2001). Stress and breast cancer. In A. Baum, T. A. Revenson, & J. E. Singer (Eds.), *Handbook of health psychology* (pp. 747–756). Mahwah, NJ: Lawrence Erlbaum Associates.

Ehlers, A., & Clark, D. M. (2000). A cognitive model of posttraumatic stress disorder. *Behaviour Research and Therapy*, *38*, 319–345.

Epping-Jordan, J. E., Compas, B. E., Osowiecki, D. M., Oppedisano, G., Gerhardt, C., Primo, K., & Krag, D. N. (1999). Psychological adjustment in breast cancer: Process of emotional distress. *Health Psychology*, *18*, 315–326.

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. *American Journal of Preventive Medicine*, *14*(4), 245–258.

Fergusson, D. M., Horwood, L. J., & Woodward, L. J. (2000). The stability of child abuse reports: A longitudinal study of the reporting behavior of young adults. *Psychological Medicine*, *30*, 529–544.

Foa, E. B., & Rothbaum, B. O. (1998). *Treating the trauma of rape: Cognitive-behavioral therapy for PTSD*. New York: Guilford.

Friedman, M. J., & McEwan, B. S. (2004). Posttraumatic stress disorder, allostatic load, and medical illness. In P. P. Schnurr, & B. L. Green (Eds.), *Trauma and health: Physical health consequences of exposure to extreme stress* (pp. 157–188). Washington, DC: American Psychological Association.

Gibb, B. E., Chelminski, I., & Zimmerman, M. (2007). Childhood emotional, physical, and sexual abuse, and diagnoses of depressive and anxiety disorders in adult psychiatric outpatients. *Depression and Anxiety*, *24*(4), 256–263.

Gould, D. A., Stevens, N. G., Ward, N. G., Carlin, A. S., Sowell, H. E., & Gustafson, B. (1994). Self-reported childhood abuse in an adult population in a primary care setting. *Archives of Family Medicine*, *3*(3), 252–256.

Green, B. L., Krupnick, J. L., Rowland, J. H., Epstein, S. A., Stockton, P., Spertus, I., & Stern, N. (2000). Trauma history as a predictor of psychologic symptoms in women with breast cancer. *Journal of Clinical Oncology*, *18*(5), 1084–1093.

Gurevich, M., Devins, G. M., & Rodin, G. M. (2002). Stress response syndromes and cancer: Conceptual and assessment issues. *Psychosomatics*, *43*(4), 259–281.

Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *Journal of Child Psychology and Psychiatry*, *45*(2), 260–273.

Hart, S. N., & Brassard, M. R. (1987). A major threat to children's mental health: Psychological maltreatment. *American Psychologist*, *42*(2), 160–165.

Horowitz, M., Wilner, N., & Alvarez, W. (1979). Impact of event scale: A measure of subjective stress. *Psychosomatic Medicine*, *41*, 209–218.

Horwitz, A. V., Widom, C. S., McLaughlin, J., & White, H. R. (2001). The impact of childhood abuse and neglect on adult mental health: A prospective study. *Journal of Health and Social Behavior*, *42*, 184–201.

Kendall-Tackett, K. (2002). The health effects of childhood abuse: Four pathways by which abuse can influence health. *Child Abuse & Neglect*, *26*(6–7), 715–729.

Kendall-Tackett, K., & Becker-Blease, K. (2004). The importance of retrospective findings in child maltreatment research. *Child Abuse & Neglect*, *28*, 723–727.

Knutson, J. F., & Selner, M. B. (1994). Punitive childhood experiences reported by young adults over a 10-year period. *Child Abuse & Neglect*, *18*(2), 155–166.

Koopman, C., Butler, L. D., Classen, C., Giese-Davis, J., Morrow, G. R., Westendorf, J., Banerjee, T., & Spiegel, D. (2002). Traumatic stress symptoms among women with recently diagnosed primary breast cancer. *Journal of Traumatic Stress*, *15*(4), 277–287.

Lawrence, J. W., Fauerbach, J., & Munster, A. (1996). Early avoidance of traumatic stimuli predicts chronicity of intrusive thoughts following burn injury. *Behavior Research and Therapy*, *34*(8), 643–646.

Leitenberg, H., Gibson, L. E., & Novy, P. L. (2004). Individual differences among undergraduate women in methods of coping with stressful events: The impact of cumulative childhood stressors and abuse. *Child Abuse & Neglect*, *28*(2), 181–192.

Manne, S., Glassman, M., & Du Hamel, K. (2000). Intrusion, avoidance, and psychological distress among individuals with cancer. *Psychosomatic Medicine*, *63*, 658–667.

McFarlane, A. C. (1992). Avoidance and intrusion in posttraumatic stress disorder. *Journal of Nervous and Mental Disease*, *180*(7), 439–445.

Ries, L. A. G., Melbert, D., Krapcho, M., Mariotto, A., Miller, B. A., Feuer, E. J., Altekruse, S. F., Lewis, D. R., Clegg, L., Eisner, M. P., Reichman, M., & Edwards, B. K. (Eds.). (2007). *SEER cancer statistics review, 1975–2004*. (p. 2007). National Cancer Institute. Retrieved from http://seer.cancer.gov/csr/1975_2004/on July 31

Salmon, P., Hill, J., Krespi, R., Clark, L., Fisher, J., & Holcombe, C. (2006). The role of child abuse and age in vulnerability to emotional problems after surgery for breast cancer. *European Journal of Cancer*, *42*, 2517–2523.

Schore, A. N. (2001). The effects of early relational trauma on right brain development, affect regulation, and infant mental health. *Infant Mental Health Journal*, *22*(1–2), 201–269.

Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, *7*(2), 147–177.

Silverman, A. B., Reinherz, H. Z., & Giaconia, R. M. (1996). The long-term sequelae of child and adolescent abuse: A longitudinal community study. *Child Abuse & Neglect*, *20*(8), 709–723.

Silvern, L., Waelde, L. C., Baughan, B. M., Karyl, J., & Kaersvang, L. L. (2000). Two formats for eliciting retrospective reports of child sexual and physical abuse: Effects on apparent prevalence and relationships to adjustment. *Child Maltreatment*, *5*(3), 236–250.

Spertus, I. L., Yehuda, R., Wong, C. M., Halligan, S., & Seremetis, S. V. (2003). Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. *Child Abuse & Neglect*, *27*(11), 1247–1258.

Stovall-McClough, K. C., & Cloitre, M. (2006). Unresolved attachment, PTSD, and dissociation in women with childhood abuse histories. *Journal of Consulting and Clinical Psychology*, *74*(2), 219–228.

Teicher, M. H., Samson, J. A., Polcari, A., & McGreenery, C. E. (2006). Sticks, stones, and hurtful words: Relative effects of various forms of childhood maltreatment. *American Journal of Psychiatry*, *163*(6), 993–1000.

Thombs, B. D., Bennett, W., Ziegelstein, R. C., Bernstein, D. P., Scher, C. D., & Forde, D. R. (2007). Cultural sensitivity in screening adults for a history of childhood abuse: Evidence from a community sample. *Journal of General Internal Medicine*, *22*(3), 368–373.

Walker, E. A., Gefland, A., Katon, W. J., Koss, M. P., von Korff, M., Bernstein, M., & Russo, J. (1999). Adult health status of women with histories of childhood abuse and neglect. *American Journal of Medicine*, *107*(4), 332–339.

Yoshihama, M., & Horrocks, J. (2002). Posttraumatic stress symptoms and victimization among Japanese American women. *Journal of Clinical Psychology*, *70*(1), 205–215.

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Clinical Study

Conducting Molecular Epidemiological Research in the Age of HIPAA: A Multi-Institutional Case-Control Study of Breast Cancer in African-American and European-American Women

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Breast cancer in African-American (AA) women occurs at an earlier age than in European-American (EA) women and is more likely to have aggressive features associated with poorer prognosis, such as high-grade and negative estrogen receptor (ER) status. The mechanisms underlying these differences are unknown. To address this, we conducted a case-control study to evaluate risk factors for high-grade ER- disease in both AA and EA women. With the onset of the Health Insurance Portability and Accountability Act of 1996, creative measures were needed to adapt case ascertainment and contact procedures to this new environment of patient privacy. In this paper, we report on our approach to establishing a multicenter study of breast cancer in New York and New Jersey, provide preliminary distributions of demographic and pathologic characteristics among case and control participants by race, and contrast participation rates by approaches to case ascertainment, with discussion of strengths and weaknesses.

1. Introduction

1.1. Rationale for the Study. Although breast cancer incidence is higher overall in women of European descent than in women of African ancestry, African-American (AA) women are more likely than European-American (EA) women to be diagnosed before age 40 and to have breast tumors with more aggressive features, including high-grade and negative estrogen receptor (ER) status (reviewed in [1]). There are no facile explanations for these differences in the epidemiology of breast cancer by ancestry. There have been several studies of breast cancer risk that include both AA and EA women, such as the Carolina Breast Cancer Study, the CARE Study, and the Black Women's Health Study; however, none were specifically designed and powered to evaluate numerous risk factors for early/aggressive breast cancer and to evaluate the distribution of these risk factors within and across racial/ethnic groups. Because of the large, racially mixed population of women in metropolitan New York City (NYC) and eastern New Jersey (NJ), we are currently conducting a case-control study, the Women's Circle of Health Study (WCHS), with the goal of accruing 1200 AA and 1200 EA women with breast cancer and an equal number of controls, to specifically address these questions. Initial funding for this study was through a Center of Excellence for Biobehavioral Breast Cancer Research (Bovbjerg, PI) focusing on AA women, funded by the Department of Defense (DOD). Additional R01 funding (Ambrosone, PI) from the National Cancer Institute (NCI) was subsequently obtained which allowed us to increase the sample size and to extend the study to EA women. Additional facets of the study are funded by the Breast Cancer Research Foundation.

2. Materials and Methods

As illustrated in Figure 1, the study has included two bases for recruitment and interviewing, one in NYC, based at Mount Sinai School of Medicine (MSSM), and one in NJ, based at The Cancer Institute of New Jersey (CINJ), with data and biospecimens sent to Roswell Park Cancer Institute (RPCI) in Buffalo, NY, for processing and storage. In the NYC metropolitan region, there are more than 60 hospitals where surgery for breast cancer is performed. When this study began in 2003, to maximize efficiency, we targeted the hospitals that had the greatest referral patterns for AA women in the boroughs of Manhattan, Brooklyn, Queens, and the Bronx. Our initial plan was to employ the approach commonly used in case-control studies, such as the Carolina Breast Cancer Study [2] and the Long Island Breast Cancer Study Project [3], wherein rapid case ascertainment is used to identify women newly diagnosed with breast cancer through periodic review of pathology reports in the targeted hospitals. When women with breast cancer are identified, a letter is sent to the treating physician, notifying them that unless they object, the patient will be contacted to describe the study and assess interest in participation.

We were unable to use this approach, however, due to the implementation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in 2003, while we were establishing the infrastructure for the study. This extension of the HIPAA regulation prevents the release of private health information (PHI) without consent from the patient. For our research purposes, this Act prevented the identification of eligible cases without the patients' prior permission given to their doctors. Although there may be situations in which an HIPAA waiver can be obtained to circumvent the need to obtain patient permission for release of identifying information to researchers [4, 5], the several participating hospitals and their Institutional Review Boards (IRB), many not extensively familiar with epidemiological research, would not grant these waivers to allow patient identification. Thus, we developed a procedure for patient ascertainment and contact that complied with the regulations of HIPAA.

As an alternative strategy, we expanded our catchment area to include eastern NJ, by partnering with CINJ and the NJ State Cancer Registry, a Surveillance, Epidemiology and End Results Program (SEER) site, housed at the NJ State Department of Health and Senior Services (NJDHSS). The study has been approved by the IRB at RPCI, Robert Wood Johnson Medical School (for The CINJ), MSSM, the individual hospitals in NYC, and the NJDHSS.

In this paper we report on both of our approaches to case ascertainment and consenting, discussing effort and costs associated with each methodology. Currently, recruitment efforts are focused only in NJ, and accrual has been discontinued in NY. We also present an overview of the study design, report on distributions of demographic and selected breast cancer risk factors among both cases and controls by race/ethnicity, and compare clinical breast cancer characteristics between groups in a subset of the population enrolled to date.

2.1. Hospital-Based Case Ascertainment and Contact: New York City. AA and EA women, 20 to 65 years of age, with no previous history of cancer other than nonmelanoma skin cancer, diagnosed within 9 months with primary, histologically confirmed invasive breast cancer or ductal carcinoma in situ who speak English were eligible for participation in the study. They were ascertained from designated hospitals that have large referral patterns for AA women in the NYC boroughs (Manhattan, Bronx, Brooklyn, and Queens; due to few AA breast cancer patients, Staten Island was not included). To maintain comparability between cases and controls, women with breast cancer must have had a residential telephone given that controls were ascertained

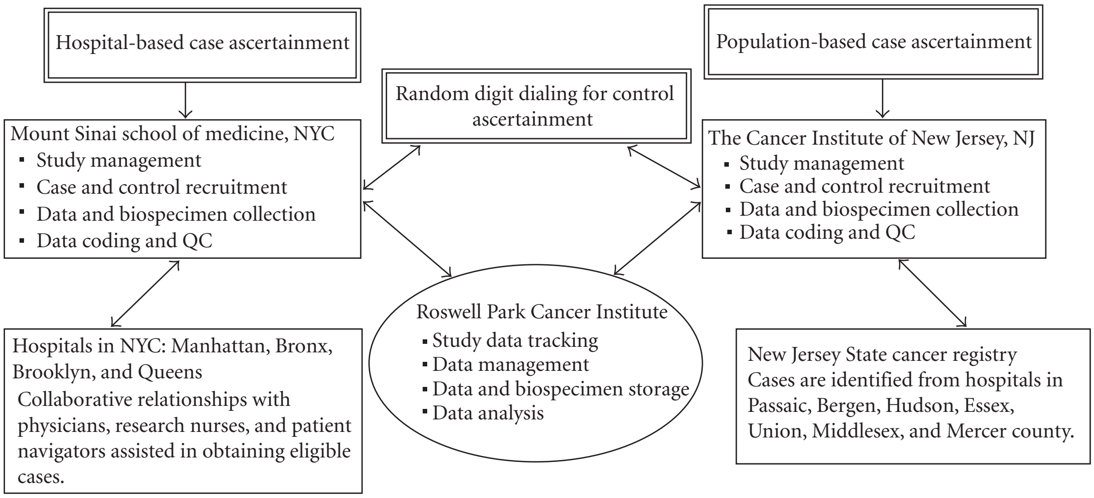

Figure 1: Organization and administration of the Women's Circle of Health Study.

using random digit dialing (RDD). This eligibility criterion has now been expanded to cell phone usage, however, with RDD also covering cell phones for control ascertainment.

To address HIPAA regulations that prohibit identification of women with breast cancer using pathology reports, tumor registry data, or medical records, we worked to develop collaborative relationships with physicians, research nurses, and patient navigators at each of the participating hospitals. Our research assistants initiated frequent visits to each site, particularly on clinic days, and became well known by staff and clinic personnel. As we began working with physicians at each site, clinicians reviewed their records for retrospective ascertainment and identified women who were eligible to be in the study (e.g., had been diagnosed within the last 9 months). At each of the participating hospitals, physicians telephoned women who were not returning for followup and would not be seen at subsequent visits, asking if WCHS staff could contact them regarding the study. Those scheduled for routine followup appointments within the 9-month interval were seen and asked if they were willing to be contacted for this study. For contemporaneous recruitment, our study staff was present in the offices on breast clinic days and was informed by the physicians or research nurses at that time of patients scheduled on those days who were eligible for the study. Study materials were placed in the charts of the eligible patients as a reminder for the clinician to discuss the study. If in agreement, the patient was then referred to our waiting study staff. A number of patients participated in the informed consent procedures at the time that they were first approached and a pretreatment blood specimen was obtained. Other women preferred to be contacted at a later date by the Research Assistant (RA)/Study Interviewer, to schedule a date to obtain consent and conduct the in-person interview.

To strive for complete case ascertainment, we periodically requested that physicians review their records to confirm that we had not missed potential cases, and that they follow the procedures described above if there were women who were not previously approached to participate in the study. It was our intent that this periodic review would allow us to estimate a denominator, to some extent, and to keep track of women who refused to be contacted so that selection bias could be examined. However, these data were not easily obtained with our inability to access records of women diagnosed who had not been approached, and competing priorities of busy surgeons.

This approach to case ascertainment and contact yielded good participation rates for both AA and EA cases but was extremely labor intensive, requiring frequent communications between our research staff and clinical personnel as well as the presence of RAs at the hospitals on clinic days. Besides being costly in personnel time, this methodology required a good deal of dedication and commitment on the part of physicians, with frequent reminders from study staff for them to check their appointment ledgers and contact patients who may have been missed on clinic days. Because of all of the limitations of this approach, in 2006 we established collaboration with the New Jersey State Cancer Registry, based at the NJDHSS for rapid case ascertainment, and phased out recruitment in metropolitan New York, ending in December 2008.

2.2. Population-Based Case Ascertainment and Contact: New Jersey. In NJ, cases are actively being identified at all major hospitals in Passaic, Bergen, Hudson, Essex, Union, Middlesex, and Mercer Counties through rapid case ascertainment. In addition, NJDHSS study staff routinely check the New Jersey State Cancer Registry (NJSCR) database for eligible cases who reside in the target counties but are reported by hospitals outside of those seven counties or out-of-state. All AA women less than 65 years of age who are newly diagnosed with incident breast cancer are identified as potential participants. For each AA case, an EA woman with breast cancer is randomly selected, matching on age (± 5 years) and county of residence. NJDHSS study staff review pathology reports of potential cases, contact doctors' offices, and hospitals to verify patients' race and demographics and check the NJSCR database for prior diagnoses of cancer. After contact with clinicians by NJDHSS staff for passive consent (e.g., contact from physician only in the event that they do not give permission to contact their patients), eligible women are telephoned by NJDHSS staff to obtain verbal consent to release names and contact information to WCHS research staff at CINJ. Patients who agree to be contacted by WCHS study staff are then telephoned by one of our interviewers, and appointments are scheduled for in-person interviews at home or at another mutually convenient location.

2.3. Control Eligibility and Identification: New York City and New Jersey. AA and EA women 20 to 65 years of age without a history of any cancer diagnosis other than non-melanoma skin cancer are eligible to be controls. The choice of a proper control group is a difficult issue in epidemiology today, particularly for a study that is not population-based. When planning for the WCHS, we evaluated several potential sources of control groups, weighing the strengths and weaknesses for each. While we considered using hospital controls in NYC, we felt that they would not necessarily represent the same populations from which the cases were derived. For example, many of the treating physicians at MSSM have private surgical practices; there is no indication that clinic patients from the hospital would be similar to those being treated by private physicians. Furthermore, there are well-recognized potential biases associated with the use of hospital controls [6]. In theory, the generalizability of study results is likely to be greater in studies using community controls rather than those using friend or hospital controls. Yet, in contrast to the Western European national health care records, none of the available United States (US) lists, such as that of licensed drivers, municipal tax roles, voter registration, and listed phone numbers, provide complete source population enumeration. Population coverage, access to this information, and the quality of contact information vary geographically in the US. Of NYC residents, it is estimated that only 52.1% have drivers licenses [7], only 30.2% pay residential taxes [8], and only 56.2% are registered voters [9]. These examples typify the acknowledged weaknesses of US and NYC sampling frames.

For generating a control group of adults under 65 years of age we used random digit dialing (RDD) because unlisted numbers can be reached by this method, thereby avoiding possible selection bias (NYC study found that 27% of RDD controls had unlisted numbers [10]). Thus, RDD provides an ideal source when phone coverage is near complete; 93% of NYC residences have phones [11]. High phone coverage makes RDD one of the best sources for generating a sampling frame for controls of NYC area women under 65 years of age. Even when the source population is not solely defined by geography, a modified version of RDD is available that creates a control sampling frame using the cases' telephone numbers [10, 12]. This is the approach that was used in the WCHS in NY. RDD controls have been compared to a privately conducted census population [13] as well as to area survey controls [14], and both comparisons found that RDD controls were similar to those from other sources. Most importantly, high response rates within a minority community were demonstrated using the modified Waksberg RDD method [15], and in the WCHS, response rates among minorities are similar to those among EA women. The elimination of household landline phones in favor of cell phones represents a challenge for telephone surveys based on RDD to landline telephones [16, 17]. However, because the percentage of households without landlines remains low [17], any potential bias associated with this issue is likely to be small. Furthermore, once subjects agree to participate in the study, cell phones tend to facilitate scheduling interviews and completing study materials because the calls go directly to the participants and are not screened by other household members.

For RDD in NYC, the telephone exchanges (area code plus three-digit prefixes) of the breast cancer cases who received medical care at the participating hospitals in previous years were used for sampling. We frequency matched controls to cases on the expected breast cancer case distribution (based on 1994–1998 data from the NYS Tumor Registry) by 5-year age groups and race. The age distribution of targeted controls was periodically modified based upon the actual distributions of age among the cases. Controls were identified, recruited, and interviewed in the same manner and during the same time period as the cases to eliminate any bias related to secular trends or changes over the interviewing period.

In NJ, the same methodology is used for ascertainment of eligible controls; however, rather than using telephone numbers from participating hospitals, the entire county is sampled, because cases include those from all hospitals in the seven targeted counties. Controls, once identified, are contacted to schedule an in-person interview; interviews are conducted either at the participant's home or at another convenient location.

For both cases and controls in NYC and NJ who decline participation, we request that they complete a short telephone interview (5–10 minutes) to obtain basic information on demographic and exposure factors. In the final analysis, data from women who refused study participation will be compared to data from women who completed an interview to evaluate potential bias related to non-participation. Women who complete the study are offered a $50 gift certificate to one of several local stores as incentive for participation. We had initially offered $25 at the beginning of the study, but later increased the amount due to inflation and efforts to increase participation.

2.4. Data Collection—Interviews and Specimen Collection. The in-person interview consists of the informed consent process, an in-depth in-person interview, completion of several behavioral questionnaires including a Food Frequency Questionnaire (FFQ), collection of biospecimens, and body measurements. For cases, we also request a release for access to medical records, pathology data and for tumor tissue, as well as permission to conduct followup.

The survey instrument is an adaptation of several questionnaires, including validated surveys from the Women's Health Initiative and the Western New York Diet Study. Developmental history questions were taken from the Women's Interview Study of Health (WISH) [18], and lifetime physical activity is assessed using a modified version of Friedenreich's validated questionnaire [19]. Information on medical history, family history of cancer, lifestyle factors including smoking, alcohol consumption, and use of hair products is also collected. The most recent version of the FFQ developed at Fred Hutchinson Cancer Center and validated in the NCI/SWOG Prostate Cancer Prevention Trial is used for dietary assessment. This FFQ has been validated for use in an AA population. At the end of the visit, detailed measurements of current body size are taken. Participants are asked to wear light clothing, as weight, standing height, and waist, and hip circumferences are measured. Body composition (lean and fat mass) is measured using a bioelectrical impedance analysis scale (Tanita scale). Questionnaires are coded by two separate RAs, and double data entry is performed by two separate clerks, with data managed at RPCI.

Interviews take approximately 2 hours to complete, including anthropometry measures. We initially collected blood samples which were processed and stored in the laboratory at MSSM. In 2007, to reduce costs and to facilitate participation, we transitioned to collection of saliva using Oragene Kits (DNA Genotek, Inc, Ottawa, ON, Canada) for DNA extraction. These collection kits yield large quantities of high-quality DNA, comparable to that obtained from whole blood [20, 21].

Periodically, DNA has been extracted in batches, using the DNA Genotek Inc. protocol for DNA extraction from saliva or the FlexiGene method (Qiagen Inc, Valencia, CA) for whole blood or buffy coat. DNA is evaluated for purity and concentration using a Nanodrop UV spectrophotometer to obtain A230, A260, and A280 readings, and double stranded DNA is quantitated using a PicoGreen-based fluorometric assay (Molecular Probes, Invitrogen Inc, Carlsbad, CA). Saliva specimens have been stored at room temperature until extraction, and DNA samples are stored at -80 C at RPCI.

2.5. Collection of Tumor Tissue Blocks and Clinical Data. Formalin-fixed paraffin-embedded blocks and corresponding pathology reports from patients who signed the pathology and tissue release have been retrieved from hospitals on an ongoing basis. To date, 1193 patients have agreed for release of their tumor tissue (91%), and this proportion does not vary between NJ and NY. Pathology reports are reviewed in order to identify a representative tumor block used to make the primary breast cancer diagnosis for each case. The tumor blocks are shipped to RPCI, where they are labeled and entered into the tracking database. Hematoxylin and eosin (H&E) slides are cut and reviewed by the study pathologist (HH) to determine the locations from which cores should be taken for construction of tissue microarrays (TMAs), taking punches from both tumor and normal tissues and for consistent determination of grade by one pathologist. Representative tumor tissue is also labeled and punches taken to be stored for future DNA extraction and analysis. Pathology departments that do not release blocks have instead been asked to process and cut the requested number of slides (eleven unstained $5\,\mu$ slides and six unstained $10\,\mu$ slides), which are then sent to the laboratory at RPCI. Tissue blocks and pathology reports are collected in tandem and include the abstraction of medical record data. Because the consent process includes a tissue block and medical record release form, and blocks are being requested in "real time", there has been little resistance on the part of the hospitals to provide tissue.

2.6. Challenges and Adaptations to Meet Them. In establishing the infrastructure for this study, and making efforts to conduct a study based in community hospitals in the face of stringent HIPAA and confidentiality requirements, our group brainstormed and adapted to achieve maximum case ascertainment, contact of patients, and recruitment into the study. With the help of committed and dedicated clinicians, this approach was successful at some hospitals, but not all. Clearly, it places a burden on already busy clinical practices, and it is likely that a complete denominator was not available, due to patients overlooked or deemed not suitable for participation in the study by their physician. In our experience, this is not a practical way to conduct a study and, unless one can ascertain cases through pathology reports or medical records, the costs of such efforts through local hospitals may not justify the numbers of cases able to be accrued. In contrast, by working through the NJDHSS, an NCI SEER site, we capture all cases diagnosed within a circumscribed area and truly know the denominator of the study for calculation of response rates. An additional advantage is that information on tumor characteristics is available for non-participating cases.

The trade-off is in participation rates. In NYC, when women were personally apprised of the study by their physician, response rates were relatively high, with 75% of EA and 75% of AA women completing interviews and providing blood or saliva samples. However, we have no data on the number of women who were eligible for the study and were not approached by their physician, or those who requested not to be contacted by our study staff.

When contacted by the NJDHSS, response rates are lower but still remain satisfactory. For EA women, 73% agreed to be contacted by an interviewer, and 93% of those women were interviewed and provided a saliva sample, for a total participation rate of 68%. Participation was poorer for AA women in NJ; 60% agreed to be contacted by an interviewer when telephoned by staff from the NJDHSS, and of those, 90% were enrolled into the study, for a total participation rate of 54%. We have met approximately half of our accrual goal, to date, and efforts are constantly made to improve response rates.

In NJ, the study is truly population-based. Newly diagnosed patients from all hospitals in the 7 targeted counties are ascertained and contacted by the NJDHSS. These counties provide the population to be captured by RDD as well. In NY, we focused on those hospitals with the highest referral patterns for AAs in the 5 boroughs excluding Staten Island, and it is clear that coverage was not complete. While an average of 1273 cases per year are reported in AA women in the boroughs, we were only able to ascertain approximately 67 per year through working with clinicians in

Table 1: Distribution of study participants by race, state, and case/control status as of June 2009. Numbers in tables vary, subject to status of double data entry of questionnaires and receipt and entry of pathology reports.

	Cases ($n = 1,315$)		Controls ($n = 1,097$)	
	African American	European American	African American	European American
New York City	339	342	356	336
New Jersey	284	350	93	312
Total	623	692	449	648

selected hospitals. We expect that the control sampling frame in NY results in a representative population, nonetheless, because the first three numbers of breast cancer patients seen in previous years at each hospital were used to obtain women in the same residential areas.

When confronted with difficulties in case ascertainment in NYC, we sought ways to expand eligibility criteria without compromising the integrity of the study. We initially limited eligibility for case participants to those between the ages of 20 to 64 years, primarily because of the low response rates using RDD for controls 65 years and older. In 2007, we extended the upper limit of age eligibility to 75 years for cases, but not controls. Although these older women cannot be used in case-control comparisons, they will allow for case-case analysis of younger versus older age at onset of breast cancer, in which age of the patient is the dependent variable. This will allow us to explore possible differences in study variables (e.g., aggressive versus non aggressive disease characteristics) between older breast cancer patients and younger breast cancer patients. We will also explore the possibility that such differences might differ by race/ethnicity groups and by other disease characteristics defined by pathology.

We had initially trained WCHS interviewers in phlebotomy and made consent for specimen collection a requirement of the study. Three tubes of blood were collected and processed, with straws stored with plasma, serum, red blood cells (RBC), and buffy coat for DNA extraction. Our intent was, when possible, to collect pretreatment blood samples to be able to compare biomarkers in cases and controls and for use later in studies of breast cancer prognosis. Because of the difficulties in accrual in NYC, and in planning approaches in NJ where we knew that we would not be able to coordinate specimen collection prior to initiation of cancer therapy, we decided to collect saliva as a source of DNA only, using Oragene Saliva DNA Self-Collection Kits when we began recruitment in NJ. Again, our ideal approach would be to have pretreatment blood specimens on all cases, but in the interests of cost and feasibility and what was viewed as long term utility of samples other than DNA, compromises had to be made. To date, we have serum, plasma, and RBCs banked on 261 AA and 197 EA controls as well as 198 and 147 AA and EA cases, respectively, which should provide us with capabilities to investigate, in a limited sample set, differences in biomarkers among controls only, and case control evaluations for markers that are not likely to be affected by surgery or adjuvant therapy. All other cases and controls provided saliva samples, and there are no participants in the study for whom a source of DNA is not available.

3. Results

As noted above, case ascertainment and accrual in NYC was terminated in 2008, and all efforts are now ongoing and focused on enrollment in NJ. Table 1 shows current recruitment numbers for cases and controls, by race, in NYC and in NJ. For the scope of this paper, we are reporting data on the subset of cases and controls who have questionnaire data which have been processed and verified through double data entry, which includes 858 controls and 1119 cases. In examining preliminary data through February 2009, there are notable differences by race/ethnicity among participants. Because we are still in data collection phase, we have made limited comparisons between cases and controls in this report. Rather, we have contrasted demographic and tumor characteristics among AA and EA women in our study samples. Among controls (Table 2), there are differences in country of birth, with more AAs born in the Caribbean. EAs are more likely to be married, to have graduated college, and to have employer-provided health insurance. Higher proportions of EA women have incomes above $90,000 per year and EA women have fewer pregnancies and at a later age than AAs. Rates of screening mammography are similar between AA and EA women without breast cancer (86% and 87%, resp.). Notably, AA controls are more likely to be overweight than EAs (30% versus 25%) or obese (52% versus 26%) but are less likely to use hormone replacement therapy (HRT) than EAs (15% versus 24%).

Demographic characteristics of cases (Table 3) and differences by race/ancestry are, for the most part, similar to distributions for controls in terms of birthplace, marital status, education, health insurance, and income. Twenty percent of AA women with breast cancer in our study either do not have health insurance (17%) or pay for insurance out of pocket (3%), compared to 12% of EA cases (4% with no insurance, 8% self-purchased). In contrast to controls, where use of mammography is similar by race/ancestry, only 78% of AA cases ever had a screening mammography, compared to 88% of EA women, and 51% of EA cases had their breast cancer discovered by mammography versus only 36% of AA women. There also appear to be greater differences by race/ancestry for hormonal and reproductive factors among cases than among controls. Twenty-nine percent of AA cases experienced menarche at or below age 12, compared to only 24% of EA women; these differences are not as notable among controls (27% versus 25%). African American cases also tend to have more children and at an earlier age than EA cases, similar to patterns observed among controls. As

Table 2: Characteristics of 858 controls.

	African American		European American	
	N (412)	%	*N* (446)	%
Age at interview				
<35	21	5.1	22	4.9
35–39	21	5.1	37	8.3
40–49	119	28.9	127	28.5
50–59	172	41.8	194	43.5
60–64	73	17.7	61	13.7
65+	6	1.5	5	1.1
Country of origin[1]				
United States and Canada	280	68.0	390	87.4
Caribbean countries	63	15.3	0	0
Other	69	16.7	56	12.6
Marital status[1]				
Married	143	34.9	277	62.1
Living as married	15	3.7	19	4.3
Widowed	21	5.1	17	3.8
Separated	34	8.3	15	3.4
Divorced	70	17.1	48	10.8
Single, never married or never lived as married	127	31.0	70	15.7
Highest grade of school completed[1]				
Less than 11th grade	52	12.6	7	1.6
High school graduate or equivalent	91	22.1	30	6.7
Some college	128	31.1	87	19.5
College graduate	86	20.9	156	35.0
Post-graduate degree	55	13.4	166	37.2
Health insurance (multiple choices possible)				
Medicaid[1]	70	17.0	17	3.8
Medicare[1]	17	4.1	7	1.6
Employer-provided insurance[1]	272	66.2	350	78.5
Pay for insurance out of pocket[1]	18	4.4	49	11.0
I do not have health insurance	29	7.0	23	5.2
Other	13	3.2	21	4.7
Annual income[1]				
Less than $15 000	51	13.4	15	3.6
$15 000–19 999	30	7.9	9	2.2
$20 000–24 999	25	6.5	5	1.2
$25 000–34 999	48	12.6	19	4.6
$35 000–49 999	68	17.8	42	10.2
$50 000–69 999	60	15.7	53	12.9
$70 000–89 999	45	11.8	61	14.8
$90 000 or more	55	14.4	208	50.5
BMI[1]				
Underweight	3	0.8	14	3.5
Normal	68	17.7	188	46.3
Overweight	115	30.0	100	24.6
Obese	198	51.6	104	25.6

Table 2: Continued.

	African American		European American	
	N (412)	%	*N* (446)	%
Age at menarche				
<11	40	9.7	39	8.8
11-12	71	17.3	69	15.6
12-13	90	21.9	112	25.3
13-14	99	24.1	124	28.0
14+	111	27.0	99	22.4
Number of pregnancies[1]				
No pregnancies	36	9.9	91	23.4
1 pregnancy	89	24.4	90	23.1
2 pregnancies	103	28.2	126	32.4
3 pregnancies	74	20.3	56	14.4
4 pregnancies	31	8.5	8	2.1
5 + pregnancies	32	8.8	18	4.6
Age at first pregnancy[1]				
≤19	115	35.5	18	6.1
20–24	107	33.0	65	22.0
25–29	50	15.4	80	27.0
30+	52	16.1	133	44.9
Age at menopause[1]				
Premenopausal	114	32.4	158	38.7
Perimenopausal	104	29.6	117	28.7
≤44	26	7.4	13	3.2
45–49	44	12.5	31	7.6
50+	64	18.2	89	21.8
Ever have hormone replacement therapy?[1]				
Yes	63	15.4	105	23.6
No	347	84.6	340	76.4
Ever have a screening mammogram?				
Yes	353	86.1	388	87.0
No	57	13.9	58	13.0

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between AAs and EAs.

observed for controls, AA women with breast cancer are also more likely to be overweight (31%) or obese (53%) than EA cases (26% and 26%, resp.) and are less likely to use HRT than EAs (15% versus 27%).

Of the pathology reports abstracted to date, the characteristics of tumors of women in our study are similar to those noted in literature [1]. African-American women are more likely than EA to have high-grade tumors (52% versus 32%) with ER negative (34% versus 22%) and PR negative (48% versus 34%) status. There are negligible differences by ancestry for HER2 status in our study population.

It is possible that differing methods of ascertainment and accrual could result in selection bias. We compared clinical and some epidemiological data between participants in NY and those in NJ. As shown in Table 4, AA cases from NY are more likely to have less than 11th grade education (22% versus 9%), more likely not to have health insurance (23% versus 9%), or be receiving Medicaid (21% versus 8%). Cases in NY had a lower incidence of DCIS (21% versus 13%), with invasive cancers being slightly higher (87% versus 79%). These differences may be due to the fact that, in New York, the majority of AA cases were ascertained at Kings County Hospital in Brooklyn which serves a large Caribbean community, many with low socioeconomic status, or because participation rates were higher in NY, resulting in some selection bias among those who agreed to be contacted in NJ.

For EA patients (Table 5), NY cases were more likely to be postgraduates (36% versus 22%) and but were less likely to have insurance (5% versus 2%) and receive Medicaid (4% versus 0%). Cases in NY were less likely to be obese (32% versus 22%) and had an older age at menarche (52% versus 42%).

Table 3: Characteristics of 1119 breast cancer cases.

	African American		European American	
	N (559)	%	N (560)	%
Age at interview				
<35	28	5.0	17	3.0
35–39	33	5.9	32	5.7
40–49	179	32.0	179	32.0
50–59	207	37.0	198	35.4
60–64	79	14.1	89	15.9
65+	33	5.9	44	7.9
Country of origin[1]				
United States and Canada	338	60.5	472	84.3
Caribbean countries	130	23.2	8	1.4
Other	91	16.3	80	14.3
Marital status[1]				
Married	195	35.1	354	63.5
Living as married	13	2.3	17	3.1
Widowed	37	6.7	23	4.1
Separated	49	8.8	10	1.8
Divorced	93	16.7	61	11.0
Single, never married or never lived as married	169	30.4	92	16.5
Highest grade of school completed[1]				
Less than 11th grade	94	16.8	13	2.3
High school graduate or equivalent	155	27.7	81	14.5
Some college	160	28.6	120	21.5
College graduate	98	17.5	180	32.2
Post-graduate degree	52	9.3	165	29.5
Health insurance (multiple choices possible)				
Medicaid[1]	87	15.6	13	2.3
Medicare	39	7.0	31	5.6
Employer-provided insurance[1]	328	58.7	455	81.4
Pay for insurance out of pocket[1]	18	3.2	42	7.5
I do not have health insurance[1]	95	17.0	22	3.9
Other	19	3.4	20	3.6
Annual income[1]				
Less than \$15 000	103	20.9	25	4.9
\$15 000–19 999	66	13.4	11	2.2
\$20 000–24 999	37	7.5	12	2.4
\$25 000–34 999	54	10.9	14	2.8
\$35 000–49 999	66	13.4	50	9.9
\$50 000–69 999	67	13.6	54	10.7
\$70 000–89 999	39	7.9	68	13.4
\$90 000 or more	62	12.6	273	53.9
BMI[1]				
Underweight	6	1.2	9	1.8
Normal	78	15.5	239	46.4
Overweight	156	30.9	132	25.6
Obese	265	52.5	135	26.2

Table 3: Continued.

	African American		European American	
	N (559)	%	N (560)	%
Age at menarche[1]				
<11	72	12.9	48	8.7
11-12	87	15.6	83	15.0
12-13	120	21.5	160	28.9
13-14	132	23.7	146	26.3
14+	147	26.3	117	21.1
Number of pregnancies[1]				
No pregnancies	43	8.4	117	23.9
1 pregnancy	112	21.8	101	20.7
2 pregnancies	161	31.4	166	33.9
3 pregnancies	94	18.3	68	13.9
4 pregnancies	51	9.9	24	4.9
5 + pregnancies	52	10.1	13	2.7
Age at first pregnancy[1]				
≤19	172	37.1	27	7.3
20–24	140	30.2	93	25.0
25–29	88	19.0	110	29.6
30+	64	13.8	142	38.2
Age at menopause[1]				
Premenopausal	200	43.4	207	40.8
Perimenopausal	115	24.9	97	19.1
≤44	28	6.1	20	3.9
45–49	46	10.0	54	10.6
50+	72	15.6	130	25.6
Ever have hormone replacement therapy?[1]				
Yes	82	14.8	152	27.2
No	473	85.2	406	72.8
Ever have a screening mammogram?[1]				
Yes	435	78.0	492	88.2
No	123	22.0	66	11.8
How was your breast cancer found?[1]				
Routine self-exam	144	26.0	63	11.4
Accidental self discovery	128	23.2	106	19.1
Accidental discovery by a partner	6	1.1	4	0.7
Routine physical exam by a doctor	37	6.7	42	7.6
Routine mammogram	198	35.8	283	51.0
Some other way	40	7.2	57	10.3
ER status[1]				
Positive	231	65.6	203	77.8
Negative	121	34.4	58	22.2
PR status[1]				
Positive	181	51.7	172	66.4
Negative	169	48.3	87	33.6
HER2				
Positive	83	27.7	41	20.8
Negative	217	72.3	156	79.2
Grade[1]				
Well-differentiated	35	8.6	68	20.9
Moderately differentiated	162	39.8	153	47.1
Poorly differentiated	210	51.6	104	32.0

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between AAs and EAs.

Table 4: Characteristics of 559 African American breast cancer cases.

	New Jersey		New York	
	N (226)	%	N (333)	%
Age at interview				
<40	20	8.9	41	12.3
50–59	154	68.1	232	69.7
60+	52	23.0	60	18.0
Highest grade of school completed[1]				
Less than 11th grade	20	8.9	74	22.2
High school graduate or equivalent	63	27.9	92	27.6
Some college	76	33.6	84	25.2
College graduate	43	19.0	55	16.5
Postgraduate degree	24	10.6	28	8.4
Health insurance (multiple choices possible)				
Medicaid[1]	18	8.0	69	20.7
Medicare	16	7.1	23	6.9
Employer-provided insurance[1]	169	74.8	159	47.8
Pay for insurance out of pocket	10	4.4	8	2.4
I do not have health insurance[1]	20	8.9	75	22.5
Other	10	4.4	9	2.7
BMI				
Underweight	1	0.5	5	1.6
Normal	28	14.1	50	16.3
Overweight	59	29.8	97	31.6
Obese	110	55.6	155	50.5
First degree relative with breast cancer				
Yes	37	16.4	45	13.5
No	189	83.6	288	86.5
Age at menarche				
<11	27	12.0	45	13.5
11–13	82	36.4	125	37.5
13+	116	51.6	163	49.0
ER status				
Positive	45	68.3	76	63.8
Negative	97	31.7	134	36.2
Grade				
Well-differentiated	15	8.2	20	8.9
Moderately differentiated	72	39.3	90	40.0
Poorly differentiated	96	52.5	115	51.1
Histologic type[1]				
DCIS	43	20.8	30	13.0
Invasive	164	79.2	201	87.0

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between states.

Differences between controls in NY and NJ (Tables 6 and 7) showed some similar patterns as those for cases. NY AA controls were more likely to be on Medicaid (18% versus 10%) and were more likely to be obese (55% versus 34%). Similar differences were noted for EA controls.

It is difficult to ascertain the representativeness of our participants in relation to the underlying populations they were derived from. However, we did ask those who refused to be interviewed to complete a short telephone interview. In NY, cases who refused tended to be older >49, insured, either

Table 5: Characteristics of 560 European American breast cancer cases.

	New Jersey		New York	
	N (252)	%	N (308)	%
Age at interview				
<40	18	7.1	31	10.1
50–59	166	65.9	211	68.7
60+	68	27.0	65	21.2
Highest grade of school completed[1]				
Less than 11th grade	6	2.4	7	2.3
High school graduate or equivalent	47	18.7	34	11.1
Some college	60	23.8	60	19.5
College graduate	83	32.9	97	31.6
Postgraduate degree	56	22.2	109	35.5
Health insurance (multiple choices possible)				
Medicaid[1]	0	0.0	13	4.2
Medicare	15	6.0	16	5.2
Employer-provided insurance[1]	220	87.7	235	76.3
Pay for insurance out of pocket	17	6.8	25	8.1
I do not have health insurance	6	2.4	16	5.2
Other	9	3.6	11	3.6
BMI[1]				
Underweight	2	0.9	7	2.5
Normal	98	42.6	141	49.5
Overweight	57	24.8	75	26.3
Obese	73	31.7	62	21.8
First degree relative with breast cancer				
Yes	58	23.0	83	27.0
No	194	77.0	225	73.0
Age at menarche[1]				
<11	25	10.0	23	7.5
11–13	120	48.2	123	40.3
13+	104	41.8	159	52.1
ER status[1]				
Positive	109	77.9	28	77.4
Negative	31	22.1	96	22.6
Grade				
Well-differentiated	43	22.8	25	18.1
Moderately differentiated	88	46.6	65	47.1
Poorly differentiated	58	30.7	48	34.8
Histologic type				
DCIS	56	25.2	40	27.6
Invasive	166	74.8	105	72.4

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between states.

through Medicaid, Medicare, or employee-based insurance, have never taken hormone replacement therapy, and have had screening mammograms. Similar differences were noted for cases in NJ and for controls (insured, no HRT, and higher prevalence of screening mammograms). For controls, those who refused were more likely to have employer-provided insurance. The higher participation rates of cases in NY suggest that there would be less selection bias than in NJ, particularly for AA cases, because of lower participation rates in NJ. On the other hand, the population of cases in NY

Table 6: Characteristics of 412 African American controls.

	New Jersey		New York	
	N (63)	%	N (349)	%
Age at interview				
<40	11	17.5	30	8.6
40–59	40	63.5	252	72.2
60+	12	19.0	67	19.2
Highest grade of school completed[1]				
Less than 11th grade	7	11.1	45	12.9
High school graduate or equivalent	13	20.6	77	22.1
Some college	18	28.6	110	31.5
College graduate	15	23.8	71	20.3
Postgraduate degree	10	15.9	46	13.2
Health insurance (multiple choices possible)				
Medicaid	6	9.5	63	18.1
Medicare	3	4.8	14	4.0
Employer-provided insurance	43	69.4	230	65.9
Pay for insurance out of pocket	3	4.8	15	4.3
I do not have health insurance[1]	4	6.4	25	7.2
Other[1]	5	7.9	8	2.3
BMI[1]				
Underweight	0	0.0	2	0.6
Normal	15	26.8	54	16.5
Overweight	22	39.3	93	28.4
Obese	19	33.9	179	54.6
First degree relative with breast cancer				
Yes	5	7.9	34	9.7
No	58	92.1	315	90.3
Age at menarche				
<11	6	9.5	35	10.1
11–13	26	41.3	135	38.8
13+	31	49.2	178	51.2

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between states.

is somewhat skewed towards those treated at the County Hospital, where there is a large Caribbean population.

4. Discussion and Future Directions

When embarking on the conduct of a case-control study, a number of factors should be considered with respect to methodology. Uppermost in importance is feasibility, which is often overlooked by young, eager investigators. Although we recruited and interviewed over 500 cases through hospitals in NYC, the approach was often a struggle, and there is no question that case ascertainment through collaboration with a state SEER Cancer Registry is much more efficient. Using this approach, we are currently interviewing over 60 women per month, with numbers expected to rise with additional interviewers hired. We are confident that we will reach our accrual goals within the next 24 to 36 months, with ample power to evaluate our main study hypotheses, yielding important information regarding the etiology of aggressive breast cancers among AA as well as EA women. Since initiating the study, scientific knowledge has advanced, and while our earlier aims were to categorize women according to age at onset, tumor grade, and ER status, we are currently reclassifying tumor grade based on readings from one pathologist and building TMAs with funding from the Breast Cancer Research Foundation to stain and read all tissue for ER, PR, and HER2 for assessment of triple negative breast cancers as well as cytokeratins 5 and 6 and HER1 to help classify basal-like breast cancers. The successful enrollment of cases and controls, and collection of tissue blocks, has also facilitated numerous collaborations for pooled studies to conduct genomewide association studies and to determine the extent of African admixture in relation to tumor characteristics. With tumor tissue DNA

Table 7: Characteristics of 446 European American controls.

	New Jersey		New York	
	N (124)	%	*N* (322)	%
Age at interview[1]				
<40	23	18.6	36	11.2
40–59	89	71.8	232	72.1
60+	12	9.7	54	16.8
Highest grade of school completed				
Less than 11th grade	1	0.8	6	1.9
High school graduate or equivalent	8	6.5	21	6.5
Some college	31	25.2	56	17.4
College graduate	44	35.8	112	34.8
Post-graduate degree	39	31.7	127	39.4
Health insurance (multiple choices possible)				
Medicaid	2	1.6	15	4.7
Medicare	1	0.8	6	1.9
Employer-provided insurance[1]	105	85.4	244	75.8
Pay for insurance out of pocket	12	9.7	37	11.5
I do not have health insurance	6	4.8	17	5.3
Other	3	2.4	18	5.6
BMI				
Underweight	1	0.8	13	4.5
Normal	48	41.0	140	48.6
Overweight	34	29.1	65	22.6
Obese	34	29.1	70	24.3
First degree relative with breast cancer				
Yes	15	12.1	49	15.2
No	109	87.9	273	84.8
Age at menarche				
<11	14	11.5	25	7.8
11–13	50	41.0	131	40.9
13+	58	47.5	164	51.3

[1] $P < .05$, Chi-square or Fisher's exact test, as appropriate, for differences between states.

as well as TMAs in addition to the epidemiologic data and biospecimens, we will have numerous opportunities not only to address our primary hypotheses but also to address novel hypotheses regarding ethnic/racial disparities in breast cancer incidence and mortality.

5. Conclusion

Epidemiological research has become increasingly difficult with the growing concerns regarding privacy and legal issues. To be able to address pressing issues in breast cancer research, particularly causal factors for the more aggressive breast cancers in AA women, creative strategies are required to conduct hospital and population-based studies. Partnership with SEER site is one approach for successful and complete case ascertainment and can facilitate the needed research in breast cancer disparities.

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References

[1] K. Amend, D. Hicks, and C. B. Ambrosone, "Breast cancer in African-American women: differences in tumor biology from European-American women," *Cancer Research*, vol. 66, no. 17, pp. 8327–8330, 2006.

[2] B. Newman, P. G. Moorman, R. Millikan, et al., "The Carolina Breast Cancer Study: integrating population-based epidemiology and molecular biology," *Breast Cancer Research and Treatment*, vol. 35, no. 1, pp. 51–60, 1995.

[3] M. D. Gammon, A. I. Neugut, R. M. Santella, et al., "The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer," *Breast Cancer Research and Treatment*, vol. 74, no. 3, pp. 235–254, 2002.

[4] "HIPAA Regulations Regarding Public Health Information," 45 CFR 164.512:(i)(2), 2002.

[5] D. S. Friedman, "HIPAA and research: how have the first two years gone?" *American Journal of Ophthalmology*, vol. 141, no. 3, pp. 543–546, 2006.

[6] K. J. Rothman, *Modern Epidemiology*, Lippincott-Raven, Philadelphia, Pa, USA, 2nd edition, 1998.

[7] "New York state licenses on file 2000 by county and gender," New York State Department of Motor Vehicles, 2001.

[8] "Profile of general demographic characteristics: 2000, geographic area: New York City, NY," U. S. Census Bureau, 2001.

[9] "Twenty year total of registered voters in New York City by borough," New York City Board of Elections, 2001.

[10] P. Hartge, L. A. Brinton, and J. F. Rosenthal, "Random digit dialing in selecting a population-based control group," *American Journal of Epidemiology*, vol. 120, no. 6, pp. 825–833, 1984.

[11] "1990 Census of Population and Housing, Summary Tape File 3," U. S. Census Bureau, 1990.

[12] J. F. Waksberg, "Sampling methods for random digit dialing," *Journal of the American Statistical Association*, vol. 73, pp. 40–46, 1978.

[13] S. H. Olson, J. L. Kelsey, T. A. Pearson, and B. Levin, "Evaluation of random digit dialing as a method of control selection in case-control studies," *American Journal of Epidemiology*, vol. 135, no. 2, pp. 210–222, 1992.

[14] C. Lele, E. A. Holly, D. S. Roseman, and D. B. Thomas, "Comparison of control subjects recruited by random digit dialing and area survey," *American Journal of Epidemiology*, vol. 140, no. 7, pp. 643–648, 1994.

[15] G. Marin, B. Vanoss, and E. J. Perez-Stable, "Feasibility of a telephone survey to study a minority community: hispanics in San Francisco," *American Journal of Public Health*, vol. 80, no. 3, pp. 323–326, 1990.

[16] P. Hartge, "Participation in population studies," *Epidemiology*, vol. 17, no. 3, pp. 252–254, 2006.

[17] S. J. Blumberg, J. V. Luke, and M. L. Cynamon, "Telephone coverage and health survey estimates: evaluating the need for concern about wireless substitution," *American Journal of Public Health*, vol. 96, no. 5, pp. 926–931, 2006.

[18] L. A. Brinton, J. R. Daling, J. M. Liff, et al., "Oral contraceptives and breast cancer risk among younger women," *Journal of the National Cancer Institute*, vol. 87, no. 11, pp. 827–835, 1995.

[19] C. M. Friedenreich, K. S. Courneya, and H. E. Bryant, "The lifetime total physical activity questionnaire: development and reliability," *Medicine and Science in Sports and Exercise*, vol. 30, no. 2, pp. 266–274, 1998.

[20] N. L. Rogers, S. A. Cole, H.-C. Lan, A. Crossa, and E. W. Demerath, "New saliva DNA collection method compared to buccal cell collection techniques for epidemiological studies," *American Journal of Human Biology*, vol. 19, no. 3, pp. 319–326, 2007.

[21] T. V. O. Hansen, M. K. Simonsen, F. C. Nielsen, and Y. A. Hundrup, "Collection of blood, saliva, and buccal cell samples in a pilot study on the Danish nurse cohort: comparison of the response rate and quality of genomic DNA," *Cancer Epidemiology Biomarkers and Prevention*, vol. 16, no. 10, pp. 2072–2076, 2007.

Project 1: Behavior, estrogen metabolism, and breast cancer risk: A molecular epidemiologic study

Principal Investigator: Dr. Christine Ambrosone

Introduction

Differences exist between African-American (AA) and European-American (EA) women in the incidence and nature of breast cancer (1-4). AA women are more frequently diagnosed with advanced, aggressive tumors, which have high histologic grade and are negative for estrogen and progesterone receptors (5); AA women are also more likely to be diagnosed before age 50 than EA women (3, 6, 7). It has been suggested that higher mortality and lower survival rates among AA women are in part due to factors associated with lower socioeconomic status (SES) and later stage at diagnosis (4, 8). However, in a number of studies, racial differences in survival remained after adjustment for stage at diagnosis, access to health care, treatment, comorbid illness, marital status and other pathologic and sociodemographic variables (7, 9-14). The fact that AA women have higher incidence rates of breast cancer at earlier ages, and that SES does not explain all of their higher breast cancer mortality, points to possible differences in the nature of the disease itself, a possibility for which there is beginning to be some support in the recent literature (15).

Although there are numerous disease characteristics that are associated with breast cancer prognosis (16), including stage, tumor size and nodal status, and molecular characteristics such as S-phase, mitotic index, Ki67, p53 over-expression, and HER-2 amplification, grade and estrogen receptor (ER) status are historically considered the most reliable markers of 'aggressiveness' to use in a large epidemiologic study. Disease stage (tumor size, lymph node involvement and metastases) is likely to be time-dependent and affected by numerous confounding variables related to SES, such as lack of screening and delays in diagnosis and receipt of treatment. Histologic grade, which includes the combined sum of scores for architectural grade, nuclear grade, and mitotic index (a marker of proliferation), is highly correlated with survival, and women with high-grade cancers have the lowest survival probabilities. Although grade and stage are correlated, small, early stage tumors can have high histologic grade and be ER negative and in the NCI Black/White Survival study, ER status was not associated with stage (17).

In addition to AA women being more likely to have tumors that are high grade and negative for estrogen and progesterone receptors, they often are also negative for HER-2. Although HER-2 amplification is a poor prognostic factor, lower expression of HER-2 removes the possibility of treatment with herceptin, resulting in poorer outcomes. Triple negative breast cancers have been found to be more common among women under the age of 40 and among non-Hispanic blacks (18). Furthermore, regardless of tumor stage, women with triple-negative breast cancers have been found to have poorer survival than those with other breast cancers, and non-Hispanic black women diagnosed at late stage with triple-negative disease have the poorest survival of any other group (18). The use of microarray gene expression techniques further characterized breast tumors into various subtypes, with the basal-like tumors associated with ER, PR and HER-2 negativity, and younger age at onset, as well as with shorter disease-free survival times (19-22). The addition of immunohistochemical markers for expression of cytokeratins 5/6 and/or EGFR has been used to further classify these aggressive tumor subtypes (23).

There are few facile explanations for the earlier onset and more aggressive breast cancer diagnosed among AA women (5, 24). AA women are more likely to experience menarche at an earlier age and to have higher estrogen levels than EA women (25). Thus, we hypothesized that earlier, more aggressive breast cancer may be related to earlier menarche and to lifetime hormonal exposures in this population. Both breast cancer and early menarche are also likely to be related to behavioral and reproductive factors, and to individual differences in hormone production and metabolism (26, 27).

In a case control study, we had proposed to identify 800 AA women with incident breast cancer at hospitals in NYC with the largest referral patterns for African-Americans and 800 controls using random digit dialing, with in-person interviews are conducted and blood and/or saliva specimen collected for extraction of DNA. Methods for this study have recently been recently described in detail (28, see Appendix). Briefly, we proposed to use this classic case control study design to explore relationships between risk of breast cancer and a number of factors that affect hormonal levels in women. We also proposed to study how those factors may affect age at menarche. Because there is some evidence that stressful events in early childhood result in early menarche (26), we evaluated the impact of childhood events on onset of menses. Our goal was to explore relationships between breast cancer risk and lifetime physical activity patterns, alcohol consumption, smoking, diet, weight and weight change throughout the life, early life events, and hormonal and reproductive factors, with data collected through an in-person interview. Subsequent studies will examine genetic differences in hormone metabolism. The same factors, childhood body size, physical activity and early stressful events can also be evaluated in relation to age at menarche.

There are few data to explain the earlier incidence of breast cancer and more aggressive disease among African-Americans, and results from this study help elucidate the probable link between breast cancer risk, early age at menarche, the hormonal milieu, and the factors that predict them. This study takes into account the role of behavioral factors and early childhood lifetime events as possible factors in breast cancer etiology, which has not previously been explored.

Body

Statement of Work

Task 1. Start-up and organizational tasks:

a. Develop study protocols for ascertainment of cases at each site
b. Identify, hire, and train interviewers
c. Pilot test study questionnaire and refine accordingly
d. Develop other study-related instruments and data collection forms
e. Design database for subject tracking and data entry of questionnaire and other data collection forms, incorporate logic and validity checks

Task 1 has been completed.

Task 2. Identify and recruit study subjects:

a. Identify ~1,400 incident breast cancer cases at participating hospitals through daily or weekly contact with institutions or private doctor's offices, expecting that 800 will be eligible and agree to participate.
b. Verify case eligibility and obtain physician consent to contact cases
c. Identify ~1,200 controls through the use of random digit dialing for those 20 to 64 years of age and Health Care Finance Administration rosters for those 65 to 74 years of age, expecting that 800 will be eligible and agree to participate

d. Assign unique identification number to each potential participant to be used on all study materials (to ensure confidentiality, personal identifiers will be kept separate from all other data)
e. Mail introductory letter
f. Telephone contact of potential subjects
   1) Introduce study
   2) Schedule in-person interview at a time and place that is convenient for participant

Task 2 is completed, with some changes in approach and protocol. As previously reported, we received funding from the NCI to build upon the infrastructure of this award and to enroll EA women and additional AA women, for a total of 1200 cases and 1200 controls of each race. The protocol and study questionnaire for these awards are the same. Because of the difficulties in case ascertainment through hospitals in New York due to HIPAA constraints, we established a contract with the New Jersey Department of Health (DOH), which is a SEER site, under the NCI grant. The NJ DOH performs rapid case ascertainment at hospitals in several targeted counties in eastern NJ, and conducts initial contact with cases after physician approval.

With the success of enrollment in NJ through the DOH, we then ceased enrollment in New York and exclusively recruited and enrolled participants through the seven counties of New Jersey (Passaic, Bergen, Hudson, Essex, Union, Middlesex, and Mercer). We intend to continue to include the cases and controls enrolled under the R01 in all analyses of results, including those participants accrued in NJ through the DOH. Because of the costs and logistical limitations associated with obtaining blood specimens, we changed the protocol in New Jersey and we now collect DNA using the Oragene kit for collection of saliva, which yields an excellent amount of high quality DNA.

To date, we have enrolled 758 AA women with breast cancer and 853 EA cases. There have been 723 AA and 881 EA controls interviewed as of May 15, 2010 for a total of 3,215 participants.

Task 3. Conduct in-person interviews:
a. Obtain informed consent and signed medical release form
b. Interviewer administers:
   1) Main questionnaire
   2) Block food frequency questionnaire
c. Measure height, weight, waist and hip circumference
d. Collect blood specimens

Task 3 is completed according to our original goals; however we have expanded our accrual goals as described above. Furthermore, as noted above, we now collect only saliva, due to logistical difficulties in collecting blood samples in NJ.

Task 4. Interviewer quality control:
a. Review the first batch of interviews (n~10) by each interviewer and provide feedback to each interviewer
b. Review all interview-related materials for completeness and internal consistency
c. Provide feedback to interviewers on a regular basis

d. Call back a ten percent sample of both cases and controls to validate questionnaire administration and key information collected

Task 4 is completed according to our original goals.

Task 5. Abstract pathology and breast cancer treatment information:

a. Abstract tumor specific characteristics such as tumor size, stage, grade, nodal involvement, and hormone receptor from pathology reports
b. Abstract breast cancer related treatment including surgery and prescribed adjuvant therapies from medical records and physicians' patient files

Task 5 has been completed as necessary for our original goals.

Task 6. Data entry:

a. Information obtained throughout the study (participant contact information, main questionnaire, pathology and treatment abstract form, body size measurements) will be entered as collected
b. All data will be double key entered to ensure accuracy

Task 6 is completed for data needed for the original goals of the study.

Task 7. Food frequency questionnaire data processing:

a. Food frequency questionnaires are sent for scanning and nutrient analysis
b. Data files containing raw data and nutrient information are returned to Mount Sinai on a disk

These tasks are completed for the 3215 cases and controls enrolled to date.

Task 8. Perform genotyping (Core B):

Task 8 has been completed. As samples are collected, DNA was extracted and quantified, and frozen for future use. We have just completed genotyping a panel of 384 SNPs in samples from cases and controls consistent with the goals of the study.

Task 9. Data cleaning, statistical analysis and manuscript preparation:

a. Write logic checks to determine out-of-range variable values and inconsistencies
b. Comprehensive analyses of data
c. Drafts of manuscripts
d. Manuscripts submitted

Task 9 has been completed for the original goals of the study. Data collected were ‘cleaned’ through real time investigation of outliers, logic checks, and programming performed for appropriate transformation of variables from questionnaire data by Core C (see report, below). Manuscripts have been drafted and submitted.

Key Research Accomplishments

We have recently reached critical mass in data collection, with approximately 3200 (numbers vary depending upon the specific data in the analysis) cases and controls from New York and New Jersey, available for analyses to examine several research questions. Descriptive characteristics of the study samples are shown below.

Table 1. Distribution of study participants by race, state and case/control status (May, 2010)

	Cases (n=1,611)		Controls (n=1,604)	
	African-American	**European-American**	**African-American**	**European-American**
New York City	339	340	357	337
New Jersey	419	513	366	544
Total	758	853	723	881

Table 2. Characteristics of WCHS Participants and exploratory descriptive analyses

	African-American					European-American				
	Cases		Controls			Cases		Controls		
	N (751)	%	N (677)	%	P	N (836)	%	N (879)	%	P
Age at interview					**<.0001**					**<.0001**
<30	**10**	**1.3**	**41**	**6.1**		**3**	**0.4**	**27**	**3.1**	
30-39	**72**	**9.6**	**92**	**13.6**		**68**	**8.1**	**116**	**13.3**	
40-49	**229**	**30.5**	**202**	**29.8**		**254**	**30.4**	**249**	**28.3**	
50-59	**264**	**35.2**	**232**	**34.3**		**269**	**32.2**	**355**	**40.4**	
60+	**176**	**23.4**	**110**	**16.3**		**242**	**29.0**	**131**	**14.9**	
Country of origin					**0.001**					**0.002**
United States	**488**	**65.0**	**499**	**73.7**		**716**	**85.7**	**768**	**87.4**	
Caribbean countries	**197**	**26.2**	**125**	**18.5**		**26**	**3.1**	**7**	**0.8**	
Other	**66**	**8.8**	**53**	**7.8**		**94**	**11.2**	**104**	**11.8**	
Marital status					**0.013**					**0.005**
Married	**269**	**36.0**	**247**	**36.6**		**526**	**63.2**	**599**	**68.1**	
Living as married	**13**	**1.7**	**18**	**2.7**		**20**	**2.4**	**25**	**2.8**	
Widowed	**61**	**8.2**	**32**	**4.7**		**45**	**5.4**	**19**	**2.2**	
Separated	**60**	**8.0**	**42**	**6.2**		**15**	**1.8**	**19**	**2.2**	
Divorced	**128**	**17.1**	**100**	**14.8**		**108**	**13.0**	**90**	**10.2**	
Single, never married or never lived as married	**217**	**29.0**	**236**	**35.0**		**118**	**14.2**	**127**	**14.5**	
Highest grade of school completed					**0.039**					**0.0005**
Less than 12th grade	**114**	**15.2**	**84**	**12.4**		**20**	**2.4**	**12**	**1.4**	
High school graduate or equivalent	**215**	**28.6**	**161**	**23.8**		**138**	**16.5**	**95**	**10.8**	

Some college	207	27.6	194	28.7		183	21.9	176	20.0	
College graduate	136	18.1	150	22.2		264	31.6	295	33.6	
Post-graduate degree	79	10.5	88	13.0		231	27.6	301	34.2	

	African-American					European-American				
	Cases		Controls			Cases		Controls		
	N (751)	%	N (731)	%	P	N (836)		N (879)	%	P
Health insurance (multiple choices possible)										
Medicaid	108	14.5	130	19.3	0.016	21	2.5	28	3.2	0.405
Medicare	61	8.2	37	5.5	0.045	79	9.5	12	1.4	<.0001
Employer-provided insurance	453	60.7	428	63.4	0.298	644	77.2	681	77.6	0.865
Pay for insurance out of pocket	25	3.4	24	3.6	0.833	67	8.0	65	7.4	0.625
I do not have health insurance	106	14.2	38	5.6	<.0001	32	3.8	39	4.4	0.530
Other	34	4.6	40	5.9	0.246	57	6.8	84	9.6	0.040
Annual income					0.052					0.361
Less than $15,000	131	19.6	98	15.5		36	4.8	25	3.1	
$15,000-19,999	78	11.7	53	8.4		16	2.1	15	1.8	
$20,000-24,999	47	7.0	37	5.9		20	2.6	16	2.0	
$25,000-34,999	75	11.2	66	10.5		25	3.3	27	3.3	
$35,000-49,999	92	13.8	106	16.8		73	9.6	65	8.0	
$50,000-69,999	87	13.0	97	15.4		92	12.1	87	10.7	
$70,000-89,999	58	8.7	75	11.9		108	14.3	121	14.9	
$90,000 or more	100	15.0	99	15.7		388	51.2	458	56.3	
BMI					0.641					0.504
Underweight	8	1.1	7	1.1		17	2.1	27	3.2	
Normal	115	16.0	123	18.6		360	44.4	359	42.3	
Overweight	220	30.5	193	29.1		217	26.8	231	27.2	
Obese	378	52.4	340	51.3		217	26.8	232	27.3	
Age at menarche					0.819					0.238
<11	101	13.5	82	12.1		78	9.4	68	7.8	
11-12	118	15.7	114	16.9		120	14.4	124	14.2	
12-13	169	22.5	147	21.8		249	30.0	239	27.4	
13-14	171	22.8	147	21.8		219	26.4	232	26.6	
14 +	192	25.6	186	27.5		165	19.9	209	24.0	
Number of pregnancies					0.083					0.431

No pregnancies	107	14.3	121	17.9		246	29.5	254	28.9	
1 pregnancy	158	21.1	161	23.8		137	16.4	146	16.6	
2 pregnancies	223	29.7	179	26.5		267	32.0	294	33.5	
3 pregnancies	126	16.8	117	17.3		124	14.9	135	15.4	
4 pregnancies	63	8.4	53	7.8		40	4.8	25	2.9	
5 + pregnancies	73	9.7	45	6.7		20	2.4	24	2.7	

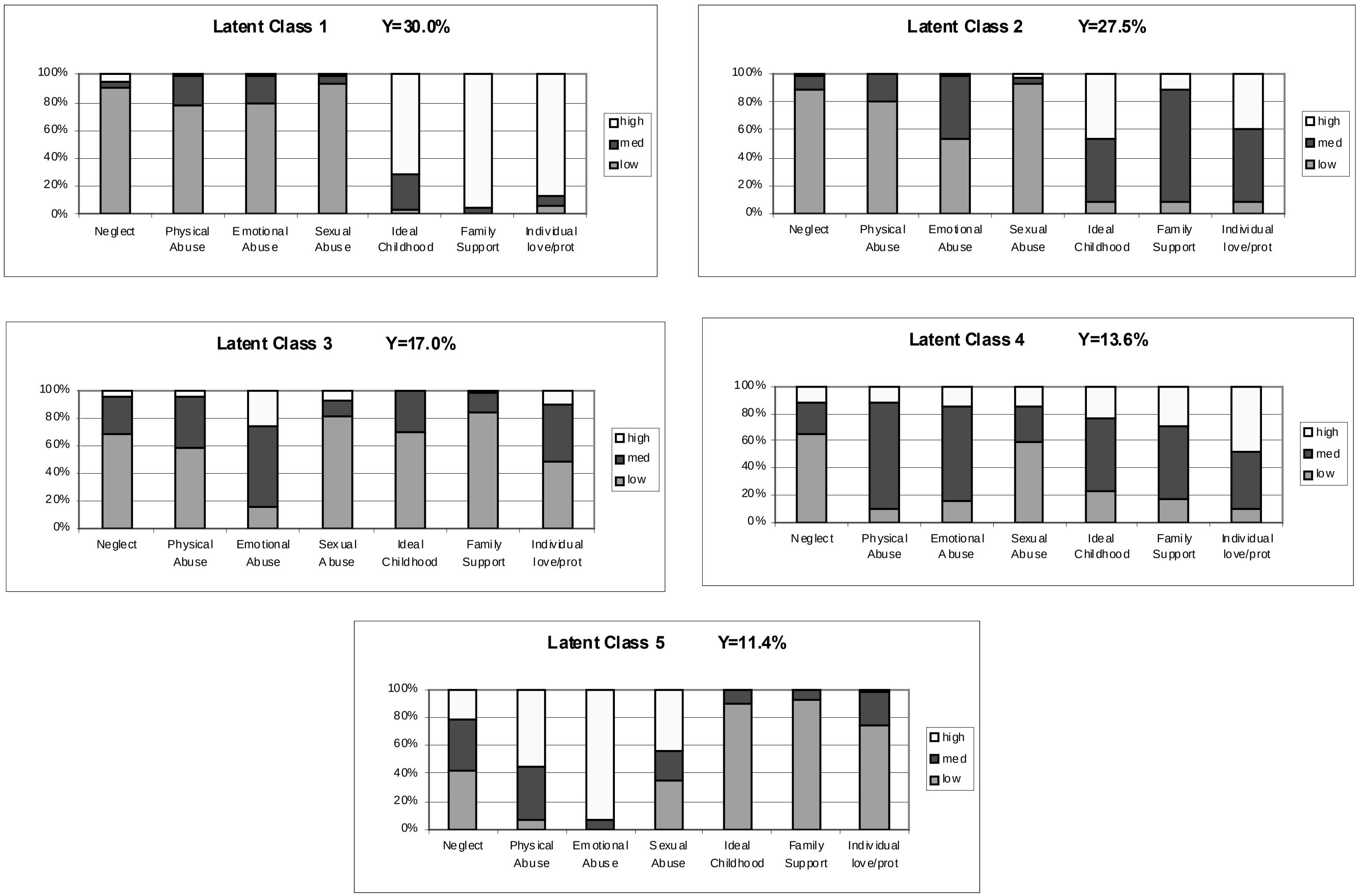
	African-American					European-American				
	Cases		Controls			Cases		Controls		
	N (751)	%	N (677)	%	P	N (836)	%	N (879)	%	P
Age at first pregnancy					0.657					0.118
≤ 19	234	36.6	210	37.9		43	7.3	36	5.8	
20-24	190	29.7	164	29.6		153	26.0	134	21.5	
25-29	113	17.7	84	15.2		174	29.6	189	30.3	
30 +	102	16.0	96	17.3		218	37.1	264	42.4	
Age at menopause					0.664					0.003
Premenopausal	272	43.5	258	44.9		302	40.0	344	42.6	
Perimenopausal	131	21.0	135	23.5		123	16.3	180	22.3	
≤ 44	52	8.3	43	7.5		38	5.0	39	4.8	
45-49	67	10.7	57	9.9		82	10.9	67	8.3	
50 +	103	16.5	82	14.3		210	27.8	178	22.0	
Ever have hormone replacement therapy?					0.283					0.009
Yes	110	14.7	86	12.8		224	26.8	188	21.4	
No	637	85.3	588	87.2		611	73.2	690	78.6	
Ever have a screening mammogram?					0.940					0.035
Yes	594	79.1	532	78.9		741	89.8	751	85.4	
No	157	20.9	142	21.1		93	11.2	128	14.6	
Family history of breast cancer?					0.088					<.0001
Yes	107	14.2	76	11.2		204	24.4	143	16.3	
No	644	85.8	601	88.8		632	75.6	736	83.7	

Table 3. Tumor Characteristics of WCHS Cases

	African-American		European-American		
	N (604)	%	N (628)	%	P
ER status					0.574
Positive	302	67.4	338	69.1	
Negative	146	32.6	151	30.9	
PR status					<.0001
Positive	239	53.8	290	69.7	
Negative	205	46.2	126	30.3	
HER2					0.0004
Positive	98	27.2	50	15.9	
Negative	263	72.8	265	84.1	
Grade					<.0001
Well-differentiated	40	8.3	106	20.3	
Moderately differentiated	192	39.6	205	45.0	
Poorly differentiated	253	52.2	146	34.7	
Tumor Type					
DCIS	110	18.2	146	23.3	
IDC	439	72.7	382	60.8	
ILC	31	5.1	49	7.8	
Invasive NOS/Other	24	4.0	51	8.1	

We have evaluated predictors of early age at menarche. Using data reduction techniques, 5 latent classes were derived for early life events, as shown below. We then examined latent classes in relation to age at menarche. Analyses indicate that only latent class 4 is associated with early age at menarche, and this group includes women who experienced some physical and emotional abuse, but also had loving support in the home. As expected, current higher BMI was associated with earlier age at menarche. Additional analyses will be conducted to place these findings into the larger context of AA breast cancer risk prior to publication.

ELE Latent Class Composition



ELE Derived Latent Clases and Age at Menarche

Logistic Regression Analysis

Caucasian Americans *(association with a younger age at menarchy)*

Charactericstic *n = 1455*	**Age at Menarche**		**Odds Ratio**	**Odds Ratio**
	< 12	*12+*	*OR (95% CI)*	*OR (95% CI)*
ELE Latent Class			*age adjusted*	*mutally adjusted*
Latent Class 1	95	344	1.0 (ref)	1.0 (ref)
Latent Class 2	116	368	1.2 (0.845, 1.568)	1.2 (0.840, 1.572)
Latent Class 3	66	218	1.1 (0.774, 1.583)	1.1 (0.750, 1.553)
Latent Class 4	34	73	1.7 (1.073, 2.733)	1.5 (0.954, 2.479)
Latent Class 5	34	107	1.2 (0.738, 1.809)	1.1 (0.698, 1.748)
BMI				
less than 25	119	554	1.0 (ref)	1.0 (ref)
25 - 30	89	299	1.4 (0.990, 1.843)	1.3 (0.985, 1.840)
30 or greater	137	257	2.4 (1.798, 3.214)	2.4 (1.752, 3.153)
Household Income				
$50,000 or greater	268	893	1.0 (ref)	1.0 (ref)
between $20,000 and $50,000	53	160	1.0 (0.743, 1.477)	1.0 (0.696, 1.404)
less than $20,000	24	57	1.4 (0.826, 2.236)	1.1 (0.678, 1.904)
Birth Weight				
less than 5 1/2 pounds	45	116	1.0 (ref)	1.0 (ref)
between 5 1/2 and 9 pounds	277	922	0.8 (0.537, 1.127)	0.8 (0.527, 1.122)
9 pounds or greater	23	72	0.8 (0.457, 1.467)	0.8 (0.425, 1.400)
Case/Control Status				
Control	174	574	1.0 (ref)	1.0 (ref)
Case	171	536	1.0 (0.774, 1.270)	1.0 (0.804, 1.333)
Age *(continuous)*				
mean	52.21	50.81		
std	10.03	9.97	1.0 (1.002, 1.027)	1.0 (0.995, 1.022)
range	(21, 76)	(20, 76)		

African Americans *(association with a younger age at menarchy)*

Charactericstic *n = 752*	**Age at Menarche**		**Odds Ratio**	**Odds Ratio**
	< 12	*12+*	*OR (95% CI)*	*OR (95% CI)*
ELE Latent Class			*age adjusted*	*mutally adjusted*
Latent Class 1	82	156	1.0 (ref)	1.0 (ref)
Latent Class 2	42	110	0.7 (0.460, 1.123)	0.7 (0.437, 1.080)
Latent Class 3	29	75	0.7 (0.432, 1.197)	0.7 (0.440, 1.230)
Latent Class 4	44	95	0.9 (0.558, 1.365)	0.9 (0.548, 1.354)
Latent Class 5	27	92	0.6 (0.331, 0.914)	0.5 (0.324, 0.908)
BMI				
less than 25	31	107	1.0 (ref)	1.0 (ref)
25 - 30	63	152	1.4 (0.880, 2.378)	1.5 (0.895, 2.440)
30 or greater	130	269	1.7 (1.084, 2.698)	1.8 (1.130, 2.850)
Household Income				
$50,000 or greater	104	234	1.0 (ref)	1.0 (ref)
between $20,000 and $50,000	67	161	0.9 (0.649, 1.352)	0.9 (0.632, 1.341)
less than $20,000	53	133	0.9 (0.606, 1.332)	0.9 (0.584, 1.320)
Birth Weight				
less than 5 1/2 pounds	33	79	1.0 (ref)	1.0 (ref)
between 5 1/2 and 9 pounds	173	418	1.0 (0.639, 1.554)	1.0 (0.606, 1.511)
9 pounds or greater	18	31	1.4 (0.688, 2.845)	1.3 (0.654, 2.780)
Case/Control Status				
Control	103	244	1.0 (ref)	1.0 (ref)
Case	121	284	1.0 (0.741, 1.392)	1.0 (0.697, 1.327)
Age *(continuous)*				
mean	51.01	51.34		
std	9.89	10.14	1.0 (0.981, 1.012)	1.0 (0.976, 1.008)
range	(24, 75)	(20, 75)		

In a second study from the larger program of research, we have investigated the potential role of vitamin D in earlier onset, more aggressive breast cancer among AA women, with partial support by funding received from the Breast Cancer Research Foundation, using data and samples from the WCHS. We measured 25-OHD levels in 242 AA and 187 EA women enrolled as controls in WCHS and adjusted for seasonality. As shown in the table to the left, there were significant differences in 25-OHD levels by race, with AA women having a mean level of 14.1 ng/ml and EA women averaging 22.2 ng/ml ($p < 0.0001$). BMI was inversely correlated with 25-OHD levels ($r=-0.38$, $p<0.0001$), and, because AA women in the WCHS had higher BMI than EA women (mean, 31.7 kg/m^2 vs 26.5 kg/m^2), we controlled for BMI in testing differences. After controlling for BMI and age, the racial differences in 25-OHD levels persisted (14.9 vs 21.4 ng/ml, $p < 0.0001$). AA women were also more likely to have severe vitamin D deficiency (<10 ng/ml) than EA women (34.3% vs 5.9%), a result similar to that seen nationally (e.g., in NHANES data). If vitamin D is related to breast cancer subtypes, these striking differences in vitamin D levels could account, in part, for disparities in breast tumor biology between AA and EA women.

Serum levels of 25-OHD by race

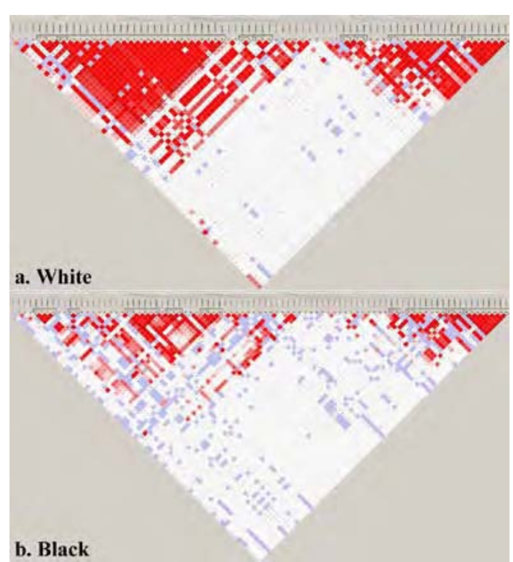
Race	Unadjusted levels, ng/ml p < 0.0001	Adjusted levels, ng/ml P < 0.0001
AA	14.1 ± 0.5	14.9 ± 0.5
EA	22.2 ± 0.7	21.4 ± 0.6

MAF of commonly studied VDR SNPs in AAs and EAs

RefID	Alias	MAF in AAs (%)	MAF in EAs (%)
rs731236	Taq1	28.6	33.6
rs7975232	Apa1	37.1	45.7
rs1544410	Bsm1	32.9	35.0
rs10735810	Fok1	23.6	42.1
rs11568820	Cdx2	20.0	27.1

In a related nested sub-study, we have examined possible racial differences in VDR genetic variations. Because of its central role in the vitamin D signaling pathway, we characterized variations in a 93.5 kb extended genetic region of the *VDR* gene by genotyping 122 SNPs in DNA samples from 70 AA and 70 EA women from WCHS. The set of high dense SNPs included not only those from the HapMap database, but also from other widely available re-sequencing databases. As shown in the figure to the right, there are clear differences in linkage disequilibrium (LD) structure of the VDR gene between AAs and EAs. In EAs, there are three major LD blocks where SNPs within each block are highly correlated, whereas in AAs, the LD blocks are shorter. We also show in the table above the differences in minor allele frequency (MAF) in the two groups of selected VDR SNPs that have been commonly studied. The distribution of the only non-synonymous SNP (rs10735810 or Fok1) of *VDR* gene is substantially different

Linkage disequilibrium map of VDR gene in AAs and EAs



between AA and EA groups (23.6% vs 42.1%). Our results clearly demonstrate racial differences in LD and genotype frequency of *VDR* gene. It is likely that similar differences exist for other genes in the vitamin D pathway, and could be related to the ultimate effects of vitamin D on breast tumor characteristics, and risk of differential subtypes between AA and EA women. In a follow-up publication, we will report on SNPs in the vitamin D receptor in DNA from 1000 of the cases and controls in the WCHS.

Reportable Outcomes

See list above

Conclusion

With supplementary funding that will continue beyond the end of the Center, the case-control study at the heart of Project 1 has initiated a program of research making substantial contributions to our understanding of the interaction between biobehavioral factors, genetics, and risk of breast cancer. With its particular focus on breast cancer among African-American women, the Project has addressed an under-studied research area of health disparities in the burden of breast cancer.

References

1) Amend K, Hicks D, Ambrosone CB: Breast cancer in African-American women: Differences in tumor biology from European-American women, Cancer Res 2006; 66:8327-30.
2) Newman LA, Martin IK: Disparities in breast cancer, Curr Probl Cancer 2007; 31(3):134-56.
3) Anderson WF, Rosenberg PS, Menashe I, Mitani A, Pfeiffer RM: Age-related crossover in breast cancer incidence rates between black and white ethnic groups, J Natl Cancer Inst 2008; 100(24):1804-14.
4) Vona-Davis L, Rose DP: The influence of socioeconomic disparities on breast cancer tumor biology and prognosis: a review, J Womens Health (Larchmt) 2009; 18(6):883-93.
5) Morris GJ, Mitchell EP: Higher incidence of aggressive breast cancers in African American women: a review, J Natl Med Assoc 2008; 100(6):698-702.
6) Cunningham JE, Butler WM: Racial disparities in female breast cancer in South Carolina: Clinical evidence for a biological basis, Breast Cancer Res Treat 2004; 88:161-76.
7) Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, Dolan NC, Paskett ED, McTiernan A, Hubbell FA, Adams-Campbell LL, Prentice R: Ethnicity and breast cancer: Factors influencing differences in incidence and outcome, J Natl Cancer Inst 2005; 97:439-48.
8) Gerend MA, Pai M: Social determinants of Black-White disparities in breast cancer mortality: a review, Cancer Epidemiol Biomarkers Prev 2008; 17(11):2913-23.
9) Li CI, Malone KE, Daling JR: Differences in breast cancer stage, treatment, and survival by race and ethnicity, Arch Intern Med 2003; 163:49-56.
10) O'Malley CD, Le GM, Glaser SL, Shema SJ, West DW: Socioeconomic status and breast carcinoma survival in four racial/ethnic groups: A population-based study, Cancer 2003; 97:1303-11.

11) Chen VW, Correa P, Kurman RJ, Wu XC, Eley JW, Austin D, Muss H, Hunter CP, Redmond C, Sobhan M: Histological characteristics of breast carcinoma in blacks and whites, Cancer Epidemiol Biomarkers Prev 1994; 3:127-35.
12) Miller BA, Hankey BF, Thomas TL: Impact of sociodemographic factors, hormone receptor status, and tumor grade on ethnic differences in tumor stage and size for breast cancer in US women, Am J Epidemiol 2002; 155:534-45.
13) Yood MU, Johnson CC, Blount A, Abrams J, Wolman E, McCarthy BD, Raju U, Nathanson DS, Worsham M, Wolman SR: Race and differences in breast cancer survival in a managed care population, J Natl Cancer Inst 1999; 91:1487-91.
14) Smith-Bindman R, Miglioretti DL, Lurie N, Abraham L, Barbash RB, Strzelczyk J, Dignan M, Barlow WE, Beasley CM, Kerlikowske K: Does utilization of screening mammography explain racial and ethnic differences in breast cancer?, Ann Intern Med 2006; 144:541-53.
15) Martin DN, Boersma BJ, Yi M, Reimers M, Howe TM, Yfantis HG, Tsai YC, Williams EH, Lee DH, Stephens RM, Weissman AM, Ambs S: Differences in the tumor microenvironment between African-American and European-American breast cancer patients, PLoS One 2009; 4(2):e4531.
16) Polyak K: Breast cancer: origins and evolution, J Clin Invest 2007; 117:3155-63.
17) Hunter CP, Redmond CK, Chen VW, Austin DF, Greenberg RS, Correa P, Muss HB, Forman MR, Wesley MN, Blacklow RS: Breast cancer: Factors associated with stage at diagnosis in black and white women. Black/White cancer survival study group, J Natl Cancer Inst 1993; 85:1129-37.
18) Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V: Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: A population-based study from the California Cancer Registry, Cancer 2007; 109:1721-8.
19) van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M, Peterse HL, van der Kooy K, Marton MJ, Witteveen AT, Schreiber GJ, Kerkhoven RM, Roberts C, Linsley PS, Bernards R, Friend SH: Gene expression profiling predicts clinical outcome of breast cancer, Nature 2002; 415:530-6.
20) Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, Johnsen H, Pesich R, Geisler S, Demeter J, Perou CM, Lonning PE, Brown PO, Borresen-Dale AL, Botstein D: Repeated observation of breast tumor subtypes in independent gene expression data sets, Proc Natl Acad Sci USA 2003; 100:8418-23.
21) Sotiriou C, Neo SY, McShane LM, Korn EL, Long PM, Jazaeri A, Martiat P, Fox SB, Harris AL, Liu ET: Breast cancer classification and prognosis based on gene expression profiles from a population-based study, Proc Natl Acad Sci USA 2003; 100:10393-8.
22) Dubsky P, Jakesz R: Dissecting the heterogeneity of breast cancer, Breast Care 2007; 2:151-56.
23) Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, Hernandez-Boussard T, Livasy C, Cowan D, Dressler L, Akslen LA, Ragaz J, Gown AM, Gilks CB, van de Rijn M, Perou CM: Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma, Clin Cancer Res 2004; 10:5367-74.
24) Axelrod D, Smith J, Kornreich D, Grinstead E, Singh B, Cangiarella J, Guth AA: Breast cancer in young women, J Am Coll Surg 2008; 206(3):1193-203.

25) Kaplowitz P: Pubertal development in girls: secular trends, Curr Opin Obstet Gynecol 2006; 18(5):487-91.
26) Mishra GD, Cooper R, Tom SE, Kuh D: Early life circumstances and their impact on menarche and menopause, Womens Health (Lond Engl) 2009; 5(2):175-90.
27) Carey LA: Through a glass darkly: advances in understanding breast cancer biology, 2000-2010, Clin Breast Cancer 2010; 10(3):188-95.
28) Ambrosone CB, Ciupak GL, Bandera EV, Jandorf L, Bovbjerg DH, Zirpoli G, Pawlish K, Godbold J, Furberg H, Fatone A, Valdimarsdottir H, Yao S, Li Yulin, Hwang H, Davis W, Roberts M, Sucheston L, Demissie K, Amend KL, Tartter P, Reilly J, Pace BW, Rohan T, Sparano J, Raptis G, Castaldi M, Estabrook A, Feldman S, Weltz C, Kemeney M: Conducting molecular epidemiological research in the age of HIPAA: A multi-institutional case-control study of breast cancer in African-American and European-American women, J Oncology; EPub 2009 Oct 25. *In press* PMC2766507

Appendices

See above

Project 2: Impact of culturally tailored counseling on psychobehavioral outcomes and BRCA decision making among women with breast cancer

Principal Investigator: Dr. Heiddis Valdimarsdottir

Introduction

<u>Hereditary Breast and Ovarian Cancer (HBOC) and Cancer Risk:</u> Accounting for 5-10% of all breast cancers and 10% of all ovarian cancers in the general population (1), prevention and treatment of hereditary forms of cancer have risen to the forefront of preventive health services in recent years, as genetic tests become available to high risk individuals with a strong family history of disease. The most common HBOC is associated with germline mutations in *BRCA1* and *BRCA2* genes (2,3) associated with a 40-66% lifetime risk of developing breast cancer, a 13-46% risk of developing ovarian cancer in unaffected women, and a 52% risk of developing a second breast cancer in breast cancer patients with a *BRCA1/2* mutation (4).

<u>Importance of *BRCA* Genetic Counseling for HBOC:</u> The U.S. Preventive Task Force (5) recommends that all at-risk individuals, defined as having at least a 10% probability of carrying a *BRCA1/2* mutation based on family history suggestive of HBOC, should undergo *BRCA* genetic counseling. Considered a prerequisite to genetic testing (6), *BRCA* genetic counseling provides women with a wealth of information including: their personal and family risk of developing breast and/or ovarian cancer; the availability of different preventive and surveillance options; and the pros and cons of undergoing *BRCA1* and *BRCA2* genetic testing. Thus, the goal of *BRCA* genetic counseling is to help women make decisions about their health care, ultimately providing life-saving cancer risk management information to prevent and/or detect cancer at its earliest, most treatable stage (6, 7).

<u>Disparities in Use of *BRCA* Genetic Counseling and Testing for HBOC among African-American women:</u> Despite the known benefits of *BRCA* genetic counseling and subsequent testing for HBOC risk, the use and underuse of these services represent one of the most potent examples of health disparities in action, as the gap widens between those who have access to and knowledge about *BRCA* genetic counseling and testing and those who do not (8, 9). Reports obtained from Myriad Genetic Laboratories show that less than 10% of the first 10,000 individuals undergoing *BRCA* genetic testing were from traditionally underrepresented racial/ethnic groups (10). Research in genetic counseling has also shown that many counselees have difficulty comprehending probability information, although some studies of genetic counseling have demonstrated gains in knowledge. However, in that research, as many as one-half of the counselees were no better informed after their counseling. Counselees demonstrated increased knowledge of *BRCA1/2* testing following genetic counseling, but the average knowledge scores were only 65% at the one-month follow-up assessment, with African-American (AA) women having the smallest increases in knowledge (11). These results may not be surprising as AA women have been found to have less prior knowledge and information about genetic testing than other women. Our research has indicated that, although AA women may be willing to provide blood samples for genetic testing, 20% of them may decline to receive their test results once they are available. This is significantly higher than the 2% refusal rate that we have observed for Caucasian women.

These findings raise the possibility that AA women may experience decisional conflict with regard to testing, even after they have undergone standard genetic counseling. One explanation for these findings may be that standard genetic counseling does not specifically address the unique concerns and attitudes that AA women have about genetic testing. As reviewed by Forman et al. (11), there is evidence that culture-specific variables play an important role in *BRCA*-decision making. For example, compared to Caucasian women, a greater proportion of AA women endorsed the following items as risks of *BRCA* testing: a) death from cancer is inevitable, b) modern medicine is not trustworthy, c) testing would be too difficult to handle emotionally, and d) testing might have a significant effect on family members. Another potential barrier to genetic testing among African-Americans may be mistrust of the medical community, as AA women have reported that suspicion influences their medical decisions in general. Genetic counseling that addresses these unique concerns may be more effective in reducing distress associated with testing which, in turn, may increase the likelihood that the counseling will be effective in increasing knowledge about genetics. Increasing knowledge about genetics may not only increase the probability that women make an informed decision with regard to testing, but it may also affect their attitudes toward surveillance and preventive options, as well as increase the likelihood that they will talk to their family members about their breast cancer risk.

The goal of the research was therefore to develop and evaluate the impact of culturally tailored genetic counseling on patient decision making regarding *BRCA* testing and subsequent cognitive, emotional, and behavioral outcomes. AA women whose family histories of cancer are suggestive of a HBOC syndrome were randomized to receive either Standard Genetic Counseling (SGC) or Culturally Tailored Genetic Counseling (CT-GC). As the CT-GC addresses culture-specific benefits and barriers to breast cancer susceptibility testing, we hypothesized that women in the CT-GC group would: 1) be more likely to elect the option that is most consistent with their personal preference; 2) report greater decisional satisfaction and less decisional conflict; 3) report less distress which, in turn, would enhance retention of knowledge and information provided in the counseling session; 4) report stronger intentions to adhere to screening guidelines and to participate in prevention options; and 5) be more likely to disseminate information provided in the counseling to their first-degree relatives.

Body

Statement of Work

Task 1 Successful application for HSRRB approval through the USAMRAA office

Task 1 has been completed.

Task 2 Develop and pilot test culturally tailored genetic counseling

Task 2 has been completed.

Task 3 Set up of Project 2 procedures and development of culturally tailored counseling

Task 3 has been completed.

Task 4 Introduction of study concepts and procedures to referring physicians, clinics, community groups through personal meetings, newsletters, newspapers, etc.

Task 4 has been completed.

Task 5 Screen and recruit study participants

Task 5 has been completed.

Task 6 Schedule study subjects and conduct baseline interviews

Task 6 has been completed.

Task 7 Randomization to study groups (SGC or CT-GC) and genetic counseling

Task 7 has been completed.

Task 8 Follow up assessment of study subjects

Task 8 has been completed.

Task 9 Data processing with double entry and resolution of discrepancies

Task 9 has been completed.

Task 10 Statistical analyses

Task 10 has been completed.

Task 11 Preparing abstracts for presentation at national meetings

Task 11 has been completed.

Task 12 Drafts of manuscripts

Task 12 has been completed.

Task 13 Submission of manuscripts to peer reviewed journals

Task 13 has been completed.

Task 14 Prepare application(s) for funding based on DOD Center procedures/results

Task 14 has been completed.

Although substantially delayed, HSRRB IRB approval through the USAMRAA office was obtained; the culturally genetic counseling was developed and tested in a randomized clinical trial; recruitment was successful due to outreach efforts; multiple papers have been published; and results have been presented at multiple conferences (See list above). Results from our longitudinal data analyses, see below, are being prepared for publication and we have received funding from the NCI to examine genetic counseling uptake among minorities (See list above).

Key Research Accomplishments

Methods: To develop the CT-GC, focus groups were conducted with AA women whose family history indicated that the cancer in their family might be inherited. As breast cancer survivors had different concerns about genetic counseling and testing than women who have never been affected by cancer, two CT-GC manuals were developed: one for women who had been diagnosed with breast cancer and one for women who had not been affected by breast cancer. Once the manuals had been developed and pilot tested, AA women at hereditary breast cancer risk were randomized to the CT-GC or to the SGC. Questionnaires assessing: 1) genetic knowledge; 2) general and cancer specific distress; 3) decisional conflict regarding genetic testing and surveillance and preventive behavior were assessed at baseline or approximately two weeks before the counseling and at follow-up or approximately one month after the genetic counseling. In addition, several potential moderating variables (e.g., acculturation, medical mistrust) were assessed in a take home packet and satisfaction with the genetic testing decision was assessed at the follow-up assessment. After the genetic counseling session, all of the women were offered the opportunity to undergo genetic testing free of charge.

Participants: One-hundred and sixty-two women completed the baseline assessment and 137 women completed both the baseline and the follow-up assessments. Of the 137 women who completed both assessments, 67 women were randomized to the SGT and 70 women were randomized to the CT-GT. The average age was 46 years (range 29 to 79 years), 32.7% of the women were married or living with a partner, 51% had an annual income of $40,000 or less, 24.37% had completed high school and 65.9% had been diagnosed with breast cancer.

Results: We have published several papers and have presented results at multiple conferences (see Reportable Outcomes above). In addition, a manuscript addressing additional hypothesized effects is being prepared. For those effects, general linear model (GLM) in SAS was used to examine the hypotheses. As CT-GC manuals differed between women who had and had not been diagnosed with cancer, we explored whether the CT-GC was equally effective for women with and without cancer diagnosis. We did not control for demographic variables as the SGC and the CT-GC groups did not differ on age, marital status, income or education (p´s >.20).

We first examined whether the counseling groups (SGC vs CT-GC) differed on the decision to undergo genetic testing. A majority of the women (N=136, 95.62%) elected to undergo genetic testing and there was no difference between the groups. The interaction between group and cancer diagnosis was not significant (p´s >.20).

We next examined whether counseling groups differed in emotional distress during the follow-up assessment or one month following the genetic counseling session. GLM was employed controlling for baseline distress values. The results for general distress, as measured by the Brief Symptom Inventory, revealed that the main effect for counseling group was significant (F=7.40, p=0.008) and the interaction between group and cancer diagnosis was significant (F=4.79, p=0.010). Simple effect analyses showed that the main effect for counseling group was significant for unaffected women (p=0.02), with women in the CT-GC group reporting lower levels of general distress than women in the SGC group, whereas the main effect for counseling group was not significant (p=0.14) for women who had been affected with cancer.

The results for cancer-specific distress, as measured by the intrusive subscale on the Impact of Event Scale, showed identical patter. The main effect for counseling group was significant (F=6.60, p=0.011) and the interaction between group and cancer diagnosis was significant (F=4.83, p=0.009). Again, simple effect analyses showed that the main effect for counseling group was significant for unaffected women (p=0.007), with women in the CT-GC group reporting lower levels of cancer specific distress than women in the SGC group, while the main effect for counseling group was not significant (p=0.17) for women who had been affected with cancer.

Reportable Outcomes

See list above

Conclusion

African-American women who have undergone culturally tailored genetic counseling have lower levels of distress following their genetic counseling than women who undergo standard genetic counseling. Surprisingly, however, the effect of culturally tailored counseling on distress was only observed among women who had not been diagnosed with cancer. Culturally tailored counseling had no effect on the women's decision to undergo genetic testing. One possible explanation for this finding is that all of the women were offered genetic counseling free of charge and almost all of the women elected to undergo testing. Based on our findings, we wrote a grant and have received funding from the NCI (R03) to examine further barriers to genetic counseling uptake among minorities and we have a pending NCI application (R21) to examine different novel interventions to increase genetic counseling uptake among minorities.

References

1) Claus EB, Schildkraut JM, Thompson WD, Risch NJ: The genetic attributable risk of breast and ovarian cancer, Cancer 1996; 77(11):18-24.
2) Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q, Cochran C, Bennett LM, Ding W, Bell R, Rosenthal J, Hussey C, Tran T, McClure M, Frye C, Hattier T, Phelps R, Haugen-Strano A, Katcher H, Yakumo K, Gholami Z, Shaffer D, Stone S, Bayer S, Wray C, Bogden R, Dayananth P, Ward J, Tonin P, Narod S, Bristow PK, Norris FH, Helvering L, Morrison P, Rosteck P, Lai M, Barrett JC, Lewis C, Neuhausen S, Cannon-Albright L, Goldgar D, Wiseman R, Kamb A, Skolnick MH: A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1, Science 1994; 266(5182):66-71.
3) Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, Collins N, Gregory S, Gumbs C, Micklem G: Identification of the breast cancer susceptibility gene BRCA2. Nature 1995; 378(6559):789-92.
4) Chen SN, Parmigiani G: Meta-analysis of BRCA1 and BRCA2 penetrance, J Clin Oncol 2007; 25(11):1329-33.
5) Nelson HD, Huffman LH, Fu R, Harris EL: Genetic risk assessment and BRCA mutation testing for breast and ovarian cancer susceptibility: systemic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2005; 143(5):362-79.
6) American Society of Clinical Oncology: American Society of Clinical Oncology policy statement updated: genetic testing for cancer susceptibility, J Clin Oncol 2003; 21(12): 2397-406.
7) Schneider KA: Genetic counseling for BRCA1/BRCA2 testing. Genet Test 1997; 1(2):91-8.
8) Hall MJ, Olopade OI: Disparities in genetic testing: thinking outside the BRCA box, J Clin Oncology 2006; 24(14):2197-2203.
9) Olopade OI: Genetics in clinical cancer care: a promise unfulfilled among minority populations, Cancer Epidemiol Biomarkers Prev 2004; 13(11):1683-6.

10) Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC: Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals, J Clin Oncol 2002; 20(6):1480-90.
11) Forman AD, Hall MJ: Influence of race⁄ethnicity on genetic counseling and testing for hereditary breast and ovarian cancer, Breast J 2009; Suppl 1:S56-62.

Appendices

See above

Project 3: Immune surveillance, stress, and inherited susceptibility to breast cancer: A psychobiological analysis of the healthy daughters of breast cancer patients

Principal Investigator: Dr. Dana H. Bovbjerg

Introduction

Healthy women with histories of breast cancer in even one first-degree relative have been found in large epidemiological studies to be more than twice as likely than women without a history of cancer in first-degree relatives to develop breast cancer themselves (1, 2). The biological mechanisms underlying that risk have yet to be fully elucidated. Less than half of the increase in risk of breast cancer among healthy women with breast cancer in one or more first degree relatives can be attributed to mutations in the well established breast cancer susceptibility genes, BRCA1 and BRCA2 (3-6).

One possible mechanism for the increased risk of breast cancer among women with family histories of the disease that has received little research attention is that these women may have inherited genetic deficits in immune surveillance mechanisms against cancer. Although highly speculative given the continuing controversy regarding the importance of immune surveillance to breast cancer risk (7), there have been have been several reports in the literature of reductions in classic surveillance mechanisms such as natural killer cell activity (8) among individuals with family histories of various cancers, including breast cancer (9-11).

The interpretation of these sporadic reports of lower natural killer cell activity, however, has been problematic for two interacting reasons. First, these studies have typically involved samples of convenience recruited though advertisements, which may well have introduced recruitment bias (e.g., attracting the "worried well"); and, second, the lower natural killer cell activity could be a secondary result of immune suppression caused by heightened psychological distress associated with having experienced breast cancer in a close relative and the knowledge of increased personal risk for the developing the disease themselves (12).

Compared to women without histories of cancer in their families, healthy adult women with family histories of breast cancer in first-degree relatives have been consistently reported to have higher levels of cancer-specific distress and, in some samples, heightened levels of general distress (12, 13). These findings raise the possibility that stress-induced suppression of immune function (14) could explain the lower levels of natural killer cell activity in this population (15, 16). Thus, the study was also designed to explore the contribution of stress-induced immune modulation (14, 17, 18) and/or inheritance of polymorphisms (19) in the genes coding for two key cytokines, interferon gamma and tumor necrosis factor alpha, to the anticipated lower level of natural killer cell activity in healthy women with family histories of breast cancer in first degree relatives.

We hypothesized that the healthy adult daughters of women with breast cancer would have lower levels of natural killer cell activity compared to daughters of control participants. We further hypothesized that these lower levels of natural killer cell activity would be associated with higher levels of psychological distress and alterations in the frequencies of particular polymorphisms in cytokine pathways.

The study was initially designed with each participating daughter assessed (Core A) on two separate occasions approximately 3 months apart at the same time of day. At each assessment, standardized self-report measures were completed and, following at least 20 minutes of quiet rest, a blood sample was collected for assessment of natural killer cell activity and DNA extraction for cytokine genotypes (Core C). Routine statistical analyses (Core B) were planned to test study hypotheses.

Body

We received HSRRB approval from the Department of Defense for this study in November, 2004. We later received approval to extend recruitment to include daughters of women who may not have participated in Project 1 ("Behavior, estrogen metabolism and breast cancer risk: A molecular epidemiologic study"), but who would have been eligible for the study. To reduce the possibility of selection bias in the study sample, we also modified the exclusion criteria. The protocol was amended to exclude the collection of blood pressure and heart rate data; instead, cortisol levels in self collected saliva samples would be used to provide an independent assessment of stress. In addition, saliva/buccal cell collection was offered as a less invasive alternative to participants who are unable to provide a blood specimen. These amendments were made in an effort to reduce participant burden.

Statement of Work:
Task 1 Successful application for HSRRB approval through the USAMRAA office

Task 1 has been completed. As noted above, after a lengthy interaction, approval was obtained.

Task 2 Setting up of Project 3 procedures

Task 2 has been completed. Based on initial experience with participants and continuing consideration of the emerging scientific literature, we proposed modifications to the procedures described in the grant application and after successful HSRRB approval those procedures were implemented.

Task 3 Screening and recruitment of study participants

Task 3 has been completed. Screening of potential study participants and recruitment of participants through signed informed consent following approved modifications to the protocol has been accomplished with the assistance of Core A.

Task 4 Inclusion of study subjects

Task 4 has been completed. Following signed consent, participants underwent their initial study assessments as described below (see Methods).

Task 5 Second assessment of study subjects

Task 5 has been completed. Women agreeing to participate in the study (signed consent) were scheduled for follow-up assessments consistent with the revised approved protocol. Based on interim review of initial data and concerns about burden as a factor contributing to difficulty in recruiting participants, the second assessment was dropped (with approval) as one of the Project tasks.

Task 6 Data processing

Task 6 has been completed as described in the original application (with the support of Core B).

Task 7 Statistical analysis

Task 7 has been completed. With the support of Core B, analyses have been conducted for both descriptive purposes and hypothesis testing to determine study outcomes and explore ancillary findings of interest relevant to the goals of the Center.

Task 8 Preparing abstracts for presentation at national meetings

Task 8 has been completed. Abstracts have been prepared, submitted and presented at national meetings (see list).

Task 9 Preparing manuscripts and/or grant application(s) as warranted based on DOD Center procedures/results

Task 9 has been completed. Multiple grant applications and manuscripts have been prepared based on Center procedures and results (see list).

While initial MSSM IRB approval of this project was received shortly after the beginning of the funding period, the HSRRB of the USAMRAA did not approve this project until November 24, 2004, which delayed the start of the project. However, with appropriate approved modifications to reduce burden while still allowing us to address critical study goals, the work was successfully conducted.

Key Research Accomplishments

Using a classic case-control study design, we have assessed the healthy daughters of breast cancer cases (meeting criteria established in Project 1 of the Center), as well as the healthy daughters of controls (healthy demographically matched women meeting criteria established in Project 1). Comparisons between these two groups allow testing of hypothesized differences.

Methods. The daughters of women meeting criteria for participation in Project 1 of the Center were recruited to constitute the two Study Groups for the proposed research: the Case-daughters Group and the Control-daughters Group. Eligibility criteria for both Groups included: age ($\geq$20), no uncontrolled major illness, sufficient facility in English to complete study questionnaires, no infectious illness within past week, no use of medication except hormone therapies, willingness to provide informed consent. Each participating Case-daughter was assessed at the same time of day, phase locked to their menstrual cycles: 1) 6-7 months following their mother's diagnosis; and, 2) three months later. Control-daughters were similarly scheduled for congruent assessments, by personnel "blind" to group status. At each assessment visit, standardized self-report measures were completed (see below) and, following at least 20 minutes of quiet rest, a blood sample (30 ml) was be collected (see below), and reimbursement offered. At the first assessment, all participants completed a standardized demographic questionnaire and medical history form. A standard battery of validated and reliable psychological instruments was then administered (10,12,13). General distress over the past 3 weeks was measured with the Brief Symptom Inventory, which assesses 9 symptom dimensions and 3 global indices of distress. Distress on the day of blood collection was assessed with the short version of the Profile of Mood States (POMS), which has been found to be related to biological sequelae of stress. Cancer specific distress (intrusive thoughts and avoidance about breast cancer) was assessed with the Impact of Event Scale. The primary study outcome was natural killer (NK) cell activity. NK cell activity in blood samples collected from study participants was determined using a classic chromium release assay with K562 tumor cell targets. These bioassays were performed in a blinded manner in the Psychoneuroimmunology Laboratory at MSSM (Bovbjerg, Director) that has documented reliability in all the proposed assessments, which were chosen to provide a systematic analysis of the multiple inputs and outputs of NK cell functions, consistent with study aims.

As shown in Table 1, the recruitment strategy yielded a diverse sample appropriate for the proposed research.

Table 1: Demographic Variables		
Age	M=33 yr; SD=9 yr; Range=18-55 yr	
Race	White	45%
	Non White	55%
Marital Status	Married /Living With Partner	40%
	Not Married (single, widowed, divorced)	60%
Education	Did Not Complete College	40%
	Completed College	60%

Analysis of the results of the psychological assessments revealed several significant differences between the Case-daughter group (healthy adult daughters of women with breast cancer meeting case participant criteria for Project 1; “Family History Positive” FH+) and the Control-daughter group (healthy adult daughters of women without breast cancer meeting control participant criteria for Project 1; “Family History Negative” FH-). These differences, while somewhat less robust than have been reported in other previous studies in the literature (13), did reach statistical significance and were thus consistent with study hypotheses.

Table 2: Psychological Variables by Family History Group:			
Dependent	**FH- Mean ± SD**	**FH+ Mean ± SD**	**Statistics**
IES: Intrusion	0.21 ± 0.54	0.58 ± 0.80	p = 0.1292
IES: Avoidance	0.27 ± 0.68	0.66 ± 0.74	p = 0.0783
IES: Avoidance +Intrusion	0.50 ± 1.23	1.25 ± 1.46	p = 0.0986
POMS Total	24.00 ± 11.03	31.02 ± 19.53	p = 0.1742
POMS: Tension	1.38 ± 2.16	3.63 ± 4.29	p = 0.0466
Perceived Risk of BC	39.64 ± 27.35	58.96 ± 25.92	p = 0.0166

Contrary to study hypotheses, we found no significant differences (or any trends toward a difference) in NK cell activity or NK cell numbers, or in NK cell activity per cell.

Table 3: Biological Variables: Natural Killer (NK) Cell Assessments			
Dependent	**FH- Mean ± SD**	**FH+ Mean ± SD**	**Statistics**
NK Cell Cytotoxicity (Mean 4 effector:target ratios)	6.64 ± 5.27	7.62 ± 10.18	p = 0.7527
NK Cell Count (CD3-CD56+)	184.43 ± 34.97	215.51 ± 77.66	p = 0.1897
NK Cell Cytotoxicity (controlling for NK cell #)	17.31 ± 4.25	19.41 ± 13.05	p = 0.5900

There are a number of possible explanations for the failure to find differences in NK cell activity between healthy women with and without family histories of breast cancer in this study. Perhaps most parsimoniously, it may be that differences simply do not exist and previous reports of such differences may have been the result of type I error. There may also have been a file drawer effect for failures to replicate. It is difficult to compare across samples to previous reports in the literature, but given the small sample sizes involved, the possible effects of stress-induced immune suppression could have contributed to previously-reported significant differences, although we clearly did not find that to be the case in the present sample. Since the primary study hypothesis for Project 3 was not confirmed, it was not appropriate to explore possible psychobiological mechanisms for differences in NK cell activity between the two study groups. That is, the proposed exploration of the contribution of polymorphisms in cytokine genes related to natural killer cell activity and the contribution of measures of distress was not appropriate to conduct.

Grounded in these null results, and the results of related studies in the laboratory, we have developed a new hypothesis of possible psychobiological contributions to the increased risk of breast cancer in healthy women with family histories of the disease. We now hypothesize that increased reactivity to acute stress (rather than the presence of chronic stress) may contribute to risk. This hypothesis is currently under investigation with the support of an R01 grant from the NCI (Bovbjerg, PI).

Reportable Outcomes

See list above

Conclusion

The study did not find support for the central hypothesis of Project 3 that deficits in immune surveillance, operationally defined by NK cell numbers and activity as assessed here, could contribute to the increased risk of breast cancer among healthy women whose mothers had breast cancer. Consistent with previous reports in the literature, healthy women with family histories of breast cancer did show some evidence of increased perception of breast cancer risk and tension/anxiety over the day prior to the assessment. These findings, as well as continuing developments in the research literature have led us to reformulate our view of how stress might contribute to increased risk of breast cancer, with an emerging focus on heightened psychobiological reactivity to acute stress as a possible risk factor.

References

1) Collaborative Group on Hormonal Factors in Breast Cancer: Familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101,986 women without the disease, Lancet 2001; 358:1389-99.
2) Couto E, Hemminki K: Estimates of heritable and environmental components of familial breast cancer using family history information, Br J Cancer 2007; 96(11):1740-2.
3) Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, Easton DF, Evans C, Deacon J, Stratton MR: Prevalence of BRCA1 and BRCA2 gene mutations in patients with early-onset breast cancer, J Natl Cancer Inst 1999; 91(11):943-9.
4) Antoniou AC, Easton DF: Models of genetic susceptibility to breast cancer, Oncogene 2006; 25:5898-5905.
5) Oldenburg RA, Meijers-Heijboer H, Cornelisse CJ, Devilee P: Genetic susceptibility for breast cancer: how many more genes to be found? Crit Rev Oncol Hematol 2007; 63(2):125-49.
6) Stratton MR, Rahman N: The emerging landscape of breast cancer susceptibility, Nat Genet 2008; 40:17-22.
7) Standish LJ, Sweet ES, Novack J, Wenner CA, Bridge C, Nelson A, Martzen M, Torkelson C: Breast cancer and the immune system, J Soc Integr Oncol 2008; 6(4):158-68.
8) Becknell B, Caligiuri MA: Natural killer cells in innate immunity and cancer, J Immunother 2008; 31:685-92.
9) Strayer DR, Carter WA, Brodsky I: Familial occurrence of breast cancer is associated with reduced natural killer cytotoxicity, Breast Cancer Res Treat 1986; 7(3):187-92.
10) Bovbjerg DH, Valdimarsdottir H: Familial cancer, emotional distress, and low natural cytotoxic activity in healthy women, Ann Oncol 1993; 4(9):745-52.

11) Montelli TC, Peracoli MT, Gabarra RC, Soares AM, Kurokawa CS: Familial cancer: depressed NK-cell cytotoxicity in healthy and cancer affected members, Arq Neuropsiquiatr 2001; 59(1):6-10.
12) Erblich J, Bovbjerg DH, Valdimarsdottir HB: Looking forward and back: distress among women at familial risk for breast cancer, Ann Behav Med 2000; 22(1):53-9.
13) Mosher CE, Danoff-Burg S: Psychosocial impact of parental cancer in adulthood: a conceptual and empirical review, Clin Psychol Rev 2005; 25(3):365-82.
14) Zachariae R: Psychoneuroimmunology: a bio-psycho-social approach to health and disease, Scand J Psychol 2009; 50:645-51.
15) Cohen M, Pollack S: Mothers with breast cancer and their adult daughters: the relationship between mothers' reaction to breast cancer and their daughters' emotional and neuroimmune status, Psychosom Med 2005; 67(1):64-71.
16) Cohen M, Klein E, Kuten A, Fried G, Zinder O, Pollack S: Increased emotional distress in daughters of breast cancer patients is associated with decreased natural cytotoxic activity, elevated levels of stress hormones and decreased secretion of Th1 cytokines, Int J Cancer 2002; 100(3):347-54.
17) Ziemssen T, Kern S: Psychoneuroimmunology--cross-talk between the immune and nervous system, J Neurol 2007; 254 Suppl 2:II8-11.
18) Costa-Pinto FA, Palermo-Neto J: Neuroimmune interactions in stress, Neuroimmunomodulation 2010; 17(3):196-9.
19) Smith AJP, Humphries SE: Cytokine and cytokine receptor gene polymorphisms and their functionality, Cytokine Growth Factor Rev 2009; 20:43-59.
20) Shakhar K, Valdimarsdottir HB, Bovbjerg DH: Heightened risk of breast cancer following pregnancy: Could lasting systemic immune alterations contribute?, Cancer Epidemiol Biomarkers Prev 2007; 16(6):1082-6.

Appendices

See above

Core A: Recruitment, Tracking and Interviewing Core

Principal Investigator: Lina Jandorf, MA

Introduction

This Core had the responsibility for contacting the identified cases, controls, and healthy adult daughters of the cases and controls, for participation in Projects 1, 2 and 3. Training for the interviewers included information on how to conduct each assessment/interview, to collect blood specimens, contact and conduct the telephone assessments for the Cases in Project 2 and the healthy adult daughters of both cases and controls for Project 3 and track their involvement across and within the project. With the additional funding of related Department of Defense projects ('Increasing Breast Cancer Surveillance Among African American Breast Cancer Survivors' [DAMD 17-03-1-0454; SIS] and 'Immune Surveillance, Cytokines, and Breast Cancer Risk: Genetic and Psychological Influences in African American Women' [DAMD 17-02-1-0501; Cytokine Study]) the staff of the core has also provided assistance with those studies.

Body

Statement of Work:

Task 1. Contact and facilitate study referrals through physicians and clinics as identified by Projects 1 and 2
Task 2. Hire and train research interviewers
Task 3. Contact participants and complete Project 1 baseline interviews Assist Project 1 in abstraction of chart review data
Task 4. Contact eligible Cases and complete Project 2 pre counseling interviews
Task 5. Track participants and complete Project 2 follow up interviews and blood draws
Task 6. Recruit participants and complete Project 3 assessments
Task 7. Responsibility for identification and resolution of tracking and data base difficulties
Task 8. Assist in the preparation of abstracts and manuscripts based on DOD Center procedures/results
Task 9. Assist in the preparation of application(s) for funding based on DOD Center procedures/results

All tasks noted in the Statement of Work have been completed.

Key Research Accomplishments

The Recruitment Tracking and Interviewing Core established systems for the identification of potential study participants, for the recruitment of participants, for getting written informed consents, and for collecting all necessary study materials including questionnaires and biological samples. The Core Laboratory worked closely with the Project PIs to ensure a high level of professionalism and reliability across the course of the research.

Reportable Outcomes

See list above

Conclusion

By providing high quality systems for recruitment, tracking and assessment of participants in the three Projects, as well as related projects that were subsequently initiated, Core A made a major contribution to the success of the Center and the research that was completed with the support of the Center.

References

None

Appendices

See above

Core B: Molecular Diagnostics and Research Core

Principal Investigator: Dr. Margaret McGovern

Introduction

The Molecular Diagnostic and Research Core of the Center for Interdisciplinary Biobehavioral Research provided expert methodological assistance to the Center regarding all aspects of the proposed molecular aspects of all of the research projects (Projects 1, 2, and 3). This assistance included not only intellectual guidance, but also practical guidance to the Projects, as well as DNA extraction and genotype processing.

The Molecular Diagnostic and Research Core worked with the individual Project PIs to identify relevant genetic risk factors in the literature, establish laboratory analyses to detect their presence in study subjects, and carry out all molecular analyses as per the individual study protocols. These analyses allowed the investigators of the Center to assess the impact of these genetic factors on cancer risks and on the psychobiology of the interaction of generic factors with family history, stress and ethnicity. The Core B Director also worked closely with the entire team of Center researchers to develop cost efficient approaches for the molecular testing.

The Core Laboratory professional staff also provided educational sessions to trainees and investigators. The Core Laboratory Principal Investigator offers a course each year, open to trainees and investigators. This course, entitled "Molecular Methods for the Clinical Investigator" includes a series of lectures on the application of molecular techniques in clinical investigation.

Body

Statement of Work:

Task 1. Ensure quality control procedures for DNA extraction, storage, and genotyping for all samples obtained under the DOD Center

Task 2. Review emerging literature to determine optimal processing and genotyping processing strategies for samples obtained under the DOD Center (Projects 1 & 3)

Task 3. Process Project 2 samples for clinical sequencing of BRCA 1 and BRCA2 genes

Task 4. Integration of Core laboratory into activities of training core

Task 5. Assist in the preparation of abstracts and manuscripts based on DOD Center procedures/results

Task 6. Assist in the preparation of application(s) for funding based on DOD Center procedures/results

All tasks noted in the Statement of Work have been completed.

Key Research Accomplishments

The Core Laboratory established a system for the storage and retrieval of study specimens that safeguarded confidentiality and ensured accurate retrieval. Blood samples were processed following established procedures for the isolation and storage of DNA from all consenting participants in the Projects. The Core Laboratory worked with the Project PIs in the establishment of a system for the storage of specimens in a liquid nitrogen straw system, and made samples and genetic data available to the Project PIs in a timely manner

Reportable Outcomes

See list above

Conclusion

Core B provided state-of-the art processing, storage, retrieval, and analysis of DNA samples as needed for the three Projects in the Center. In addition, the Core provided training and consultation to Center faculty and Trainees. The Core thus made a major contribution to the success of the Center and the productivity of the investigators involved (See list above).

References

None

Appendices

See above

Core C: Biostatistics and Data Management Core

Principal Investigator: Dr. James H. Godbold

Introduction

The objective of the Biostatistics and Data Management Core was to provide databases for entry, storage, and retrieval of data collected in the three projects of this Center. The quality of the data was monitored at each step in the process. The Core also provided statistical analyses of the data using appropriate models to address the specific aims/objectives of each project.

The three Projects in this Center project each collected multiple sets of interrelated data to address their study hypotheses. It was extremely important that the data that are collected be managed in a careful way and that the analyses that are performed on the data use statistics that lead to valid conclusions.

Without good management of data, cleaning of data to provide a valid dataset, and appropriate statistical analyses of the collected data, the work in three projects would be of little value. The members of this Core worked closely with the investigators of the three projects and members of the other Cores to coordinate the data activities so that this work is done in a timely manner.

Body

Statement of Work

Task 1. Design databases for data to be collected in Projects 1, 2, and 3
Task 2. Write programs to establish databases for Projects 1, 2, and 3
Task 3. Validate databases by entering hypothetical data, some of which is correct and some of which has deliberate errors to see if the database will prevent erroneous values from being entered while allowing for entry of correct values.
Task 4. Develop tracking system for data collected in Projects 1, 2, and 3 for use in Core A
Task 5. Establish Master Logs for biological specimens
Task 6. Enter data into database for Project 1, assist with quality control for Projects 2 and 3.
Task 7. Monitor data collection activities in Projects 1, 2, and 3
Task 8. Generate regular reports on subject enrollment and data collection for use by Core A
Task 9. Generate queries for data that fail range and logic checks at time of entry to the database
Task 10. Monitor status of data queries
Task 11. Design statistical programs for data analysis for Projects 1, 2, and 3
Task 12. Write programs for final data cleaning
Task 13. Write programs in SAS to perform statistical analyses
Task 14. Test SAS programs on a preliminary data to verify the programs are performing calculations correctly
Task 15. Run data cleaning routines on databases to generate reports on subject enrollment and data entered. Generate queries on data that fail data cleaning tests. Re-enter cleaned data.
Task 16. Perform exploratory data analyses for abstracts reporting preliminary results
Task 17. Modify plans for final analyses based on results of exploratory analyses
Task 18. Assist in the preparation of abstracts and manuscripts based on DOD Center

procedures/results

Task 19. Assist in the preparation of application(s) for funding based on DOD Center procedures/results

Task 20. Generate statistical analyses of complete data for final reports and manuscripts

All tasks noted in the Statement of Work have been complete

Key Research Accomplishments

The Biostatistics and Data Management Core assisted the investigators with all relevant aspects of data entry, including double entry procedures with resolution of discrepancies. Several complex/advanced ACCESS queries were conducted for the Project 2 genetic counselor to provide the ability to better monitor progress of participants at different stages of the study. Several fields were added to the Post-interview Checklist Form and were explained to study personnel to maximize the utility of the tracking database for all researchers. A computerized procedure was used to upload and append Random Digit Dialing batches for all study site controls to the tracking database, as well as to generate mail merge contact sheets, mailing labels, and contact letters. Complex/advanced queries in MS Access were conducted for Project 3 to provide better ability to explore data available from study participants at different stages of the study as well as generate numbers for reports.

The Core also assisted investigators with analyses of cleaned data as necessary for preparation of reports, abstracts and manuscripts.

Reportable Outcomes

See list above

Conclusion

Core C provided cutting edge biostatistical and data management assistance to all three Projects in the Center, as well as to Trainee and faculty members conducting related breast cancer research. As such, the Core made a major contribution to the success of the Center and the productivity of the investigators involved (See list above).

References

None

Appendices

See above

Core D: Training Core

Principal Investigator: Dr. Dana H. Bovbjerg

Introduction

Breast cancer continues to be a preeminent cause of morbidity and mortality among American women, despite continuing encouraging news that cancer incidence and mortality rates have inched downward in the past decade. The risk of early mortality is a particularly a concern for African-American women. African-American women are more frequently diagnosed with advanced, aggressive tumors, and those under age 50 have nearly twice the breast cancer risk of white women. The research literature suggests that it is the interaction of behavioral and genetic factors, which may account for clinical findings among African-American women. However, few researchers today are equipped with the skills necessary to investigate the interactions among behavioral factors, genetics, and culture. The goal of the Training Core in Biobehavioral Breast Cancer Research was to foster the development of interdisciplinary researchers focused on epidemiological and biobehavioral aspects of breast cancer that are particularly relevant to African-Americans through a broadly based, multidisciplinary postdoctoral training program involving a required curriculum of formal lectures, participation in specialized seminar series, "hands-on" research experience with the guidance of a nationally-recognized research mentor, and formal, as well as hands-on, training in the preparation of research papers and grants. This training acted as a bridge between behavioral and epidemiological approaches to breast cancer research.

Body

Because of delays waiting for HSRRB approval for Projects 1, 2, and 3, which were intended to provide direct research experience for trainees, we had to modify the timeline in our initial Statement of Work. However, with the HSRRB approval for the Projects in place, we have been able to complete all tasks.

Tasks 1 (months 1-24) and 3 (months 24-48):
a) Recruit applications;
b) Evaluate potential trainees;
c) Develop and schedule Foundations Curriculum;
d) Coordinate training with ongoing Cancer Center Training Programs;
e) Schedule seminar series;
f) Run Foundations and Seminar Series;
g) Establish hands-on research experience for each Trainee;
h) Schedule and run Luncheon Lecture Series;
i) Guide development of independent research project for each Trainee;
j) Provide oversight for each Trainee's independent project;
k) Conduct formal evaluations of Trainees and Program;
l) Facilitate preparation of research reports and grant applications;

Tasks 2 and 4: Prepare and submit required reports for BCRP

Because of delays imposed by the HSRRB review process, Task 1, subsections g and i-l were accomplished with related research approved by the Mount Sinai Institutional Review

Board for protection of human subjects, and funded by other sources. Tasks 2 and 4 are completed with this report. We have now also accomplished Task 3, recruiting and evaluating of a second class of postdoctoral trainees. The two final trainees under this program began in the fall of 2005 and completed the training program outlined in subsections c-l, with the ability to participate in the Center research projects approved by HSSRB.

Key Research Accomplishments

The Core established effective ways to recruit, evaluate, and train the fellows as consistent with the Statement of Work. This process included not only direct mentoring, but also a training curriculum including presentations by members of the MSSM faculty. Examples from the training of the final two Trainees are provided below.

Core Courses (subsections c,d,f):

An Overview of Clinical Issues in Cancer (Core Course, 9 of 16 courses listed below)

04 Oct 2006 Dr. James Holland, "An Introduction to Clinical Oncology"

11 Oct 2006 Dr. Simon Hall, "Prostate Cancer - Etiology and Treatment"

25 Oct 2006 Dr. George Raptis, "Breast Cancer: From Soup to Nuts in 1 Hour"

01 Nov 2006 Dr. Scott Swanson, "Lung Cancer - Etiology and Treatment"

08 Nov 2006 Ms. Arden Moulton, "Patients' Perspective"

15 Nov 2006 Dr. Steve Itzkowitz, "Colorectal Cancer - Etiology and Treatment"

29 Nov 2006 Dr. Jamie Cesaretti, "Principles of Radiation Oncology"

06 Dec 2006 Dr. Peter Dottino, "Gynecological Cancer -Etiology and Treatment"

13 Dec 2006 Dr. Gabrielle Goldberg, "An Overview of Palliative Care"

03 Jan 2007 Dr. David Sternberg, "An Introduction to Chemotherapy Treatment of Cancer"

10 Jan 2007 Dr. Max Sung, "An Overview of Liver Cancer"

17 Jan 2007 Dr. Robert Phelps, "An Overview of Skin Cancer: Basal Cell Carcinoma, Squamous Cell Carcinoma and Malignant melanoma; Etiology and Treatment"

24 Jan 2007 Dr. Janice Gabrilove, "Hematological Cancer - Etiology and Treatment"

31 Jan 2007 Dr. Gordon Freeman, "An Overview of Cancer Pain"

07 February Dr. Konstantin Zakashansky, "How to Read a Clinical Paper: An Example from the Recent Literature"

Work-in-Progress presentations (subsections i,l):

21 Sept 2006 Dr. Guy Montgomery, Associate Professor, Oncological Sciences, MSSM

05 Oct 2006 Dr. William Redd, Professor, Oncological Sciences, MSSM

23 Feb 2007 Dr. Sharon Manne, Senior Member, Population Science Division, Fox Chase Cancer Center

19 Mar 2007 Dr. William Redd, Professor, Oncological Sciences, Mount Sinai School of Medicine

6 Sept 2007 Dr. Christine Rini, Professor, Oncological Sciences, Mount Sinai School of Medicine

Seminar/Lecture Series (subsections e,f,h):

20 Sept 2006 "Numeracy, affect, and health decisions," Dr. Ellen Peters, Research Scientist, Decision Research and the University of Oregon, Institute of Cognitive and decision Sciences.

17 Nov 2006 “Long term models of survivorship: Where are the research challenges?” Dr. Deborah Bowen, Fred Hutchinson Cancer Research Center/University of Washington
2 Feb 2007 “Psychological Treatment of Post-traumatic Stress Disorder” Dr. Terence M. Keane, Research and Development at Boston VA Medical Center, Boston University School of Medicine
22 Feb 2007 “Coping with disease-related pain: Issues and opportunities” Dr. Frank Keefe, Duke Pain and Palliative Care Initiative at Duke University Medical Center
3 Mar 2007 “Smoking Relapse in Women: Effect of Menstrual Phase” Dr. Sharon S. Allen, Department of Family Medicine at University of Minnesota
29 Mar 2007 “Prospective, Longitudinal Study of Fatigue in Early Stage Breast Cancer” Dr. Michael Andrykowski, Department of Behavioral Science at University of Kentucky
30 Mar 2007 “The Possibilities of Narrative Psychology for Understanding the Relationship between Personality and Health” Dr. Suzanne C. Ouellette, Doctoral program in psychology at The Graduate School CUNY
25 May 2007 “An Evidence Based Traditional Taiji Program” Dr. Yang Yang, Department of Kinesiology and Community Health at University of Illinois Urbana-Campaign

Reportable Outcomes

See list above

Conclusion

Core D successfully conducted a broad-based postdoctoral training program to prepare four Trainees for interdisciplinary research in biobehavioral approaches to breast cancer with a particular focus on minority issues. The Trainees all made contributions to the literature on breast cancer during and after their fellowship periods. Following training in the Center, they took positions consistent with their goals of developing independent research careers in this area.

References

None

Appendices

See above